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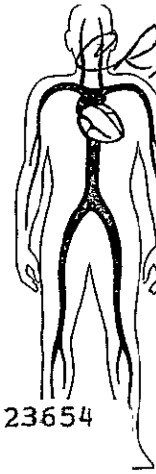

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TECHNOLOGY INCORPORATED
LIFE SCIENCES DIVISION

FINAL REPORT

ANALYSIS OF BODY FORM USING BIOSTEREOMETRICS

Contract NAS 9-15220

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FINAL REPORT

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BIOSTEREOMETRICS

Contract.NAS 9-15220

APPROVED BY:

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SECTION I

TASK DESCRIPTIONS

Work performed under Contract Number NAS 9-15220 was done in accordance with the original statement of work dated October 7, 1976 and issued in the request for proposal, revision number one dated November 1, 1977, and a final technical modification dated February 16, 1978.

The original statement of work stated the general objective of the research, "to provide the Space and Life Sciences Directorate with an improved Biostereometric Measurement Capability." This objective was determined from the usefullness of stereophotogrametric techniques developed during the Apollo and Skylab Missions to measure body conformation, surface area, volume and relative density of astronauts. These noninvasive anthropometric measurements provided invaluable data concerning the physiological, biochemical and nutritional effects of the space environment upon the human body. The indirect nature of the technique has many advantages over other methods, and has a potential for many other applications. The stereophotographs contain an enormous amount of data which can be later re-examined should the need arise.

Six directed areas of activity were delineated in the statement of work.

1. <u>Completion of Bedrest Measurements</u>
2. <u>Automation of Plotting Procedure</u>
3. <u>Development of Inflight Experiments</u>
4. <u>Anthropometric Measurements for Space Suit Fitting</u>

5. <u>Physical Examinations</u>

6. <u>Cooperative Effort With JSC</u>

Task area number one referred to the plotting and computations for data from a bedrest study conducted at the Baylor College of Medicine. Revision one to the statement of work expanded the general direction by stating that its intent was to reanalyse existing data, particularly that obtained in Skylab and in the Baylor Bedrest Study, not only to verify and extend its scope, but also to employ it as a base of reference in developing new automation procedures.

Task area number two was directed toward automation of the plotting procedure to significantly reduce the manhours required for each stereophotographic measurement and to improve its precision. The procedure used required over 8 manhours of tedious highly skilled labor. A considerable reduction in the manhour requirement would significantly enhance the utility of the technique. It was felt that the area where the greatest improvement could be realized was in automating the scanning and digitizing process.

Automation of the plotting procedures resolved into three general categories: (1) bulk digitizing and batch analysis, (2) intelligence directed digitizing and on-line analysis, and (3) video techniques.

The first of these techniques involved converting the stereo pairs into two large matrices of gray scale intensities of the form (X-coordinate, Y-coordinate,

gray scale value). These matrices can then be compared and statistically analyzed to locate the common fiducial points. The resulting data values can then be entered into the currently existing software to produce the volume and shape results.

The second technique involved the development of an on-line digitizing scanner to simultaneously scan the stereo pairs to locate the common fiducial points. Such a scanner would employ a minicomputer or microcomputer scanner to direct the motion of the two scanning arms to determine the common points. These would then be digitized as with the current manual set-up and analyzed using the existing software.

The third technique involved the use of video scanners which are commercially available. These scanners take the place of the stereo camera. Rather than analyzing a pair of photographic negatives, this technique involves the analysis of a pair of video representations of the subject.

Task area three was concerned with the development of experimental protocols for determination of subtle changes in body form during space flight. Biostereometric techniques provide a potentially highly accurate and reliable method of measuring these changes at the cost of very little crew time. Inlfight biostereometric techniques were initiated on SMS II. These techniques were to be refined with the following parameters to be measured:

a. Fluid redistribution and changes in total body fluid.

b. Abdominal distension.

c. Changes in muscle mass.

d. Changes in body density and overall fat content.

In the experiments development area, Technology Incorporated's approach was to develop new equipment utilization concepts leading to a reliable, light-weight, simple in-flight biostereometric measuring apparatus. This, coupled with the automated ground based analysis system, facilitates support of highly accurate biostereometric measurements in the space environment. Further, the automated analysis system decrease turn-around time for analysis, thus increasing the usefullness of the technique. These developments were to expand on the experience gained in SMS II and be tested on future Spacelab simulations. Improvements based on the SMS II experience were to include redesign and relocation of the cameras and object space control units into equipment racks so that preparation time is minimized and measurements can be readily accomplished.

Data obtained from simulated and real missions will describe with great accuracy and detail the whole body surface and will address the following variables: (1) fluid redistribution and fluid changes, (2) abdominal distension, (3) changes in body density leading to insight into changes in body composition, (4) changes in muscle mass, and (5) changes in body segment lengths and skeletal realignment. This in-flight measuring apparatus could concurrently be used in other experimental areas to provide an accurate record of changes in surface shape and size.

The approach of the shuttle era with its number and frequency of flights made the usual approach to custom tailoring of space suits cost-prohibitive. The

importance of task area four, anthropometric measurements for space suit fitting was established. In designing a suit to fit all Shuttle crewmembers, precise body conformation measurements of all potential users is required, both for statistical information and to guarantee that the suit will fit crewmembers with extremely large or small dimensions in any of a number of body dimensions. In acquiring this detailed three-dimensional information, biostereometric photography may provide the amount of necessary precision while requiring a minimum of the crewmember's time. In addition, a permanent record of any body dimension is available from the photograph should any new information be required at a later time. Technology Incorporated was to provide support for the precise measurement of individual crewmembers by performing the biostereometric photography and analyzing the resulting photographs.

Task five required Biostereometric support during the crew selection physical examination process. It was intended that biostereometric measurement of probable crewmembers be used as mentioned above for spacesuit fitting. It was to be stored archivally for subsequent comparison to pre-, in-, and post-flight measurements. Such archival measurements can prove invaluable to investigators as Spacelab becomes a reality. Automated analysis of the biostereometric pairs will allow biostereometric measurements to be economically performed on prospective crewmembers without excessive time devoted to the manual reduction of the data.

Task area six required coordination and interface with the Systems and Facilities Branch of the Earth Observations Division with regard to the utilization

of specialized procedures and equipment. Operation of semi-automated plotting facilities was a priority effort revision 1, Exhibit "A", previously mentioned, changed the scope of the effort on Analysis of Bedrest Data (already discussed), and the interjection of tasks associated with computerized tomography. Specifically, the tasks were to evaluate the use of computerized tomography to detect skeletal changes precipitated by bone demineralization during prolonged exposure to simulated and actual spaceflight, and to utilized gamma ray computer tomography for the determination of spongy bone density. The technique was to be used directly in evaluating the results of the biostereometrics, measurements of changes resulting from reduced mobility programs such as the bed rest studies being done in conjunction with the U. S. Public Health Service.

Exhibit "B", dated February 16, 1978 directed the continued pursuit of assessment of the adequacy of gamma ray computerized tomography as a sensitive tool for the measurement of trabecular bone density. Other directed work included:

... Consolidation within a single working area of all measurement devices and associated equipment being utilized for the analysis of body form and the measurement of bone density.

... Review of data that has been accumulated and become thoroughly familiar with the methods that have been used to assess the effects of space flight and bed rest upon bone structure.

... Set-up the gamma ray computerized tomograph so that is will be in operaing order and demonstration of the attainment of this objective with appropriate test measurements.

... Conduct such comparative tests as are necessary to establish the efficacy of gamma ray computerized tomography as a method for measuring changes in bone density. The new method will be compared to the one employed by Vogel and associates. The contractor will be expected only to apply the measurement procedure. Subjects and the experimental condition of bedrest will be furnished in conjunction with other on-going efforts.

... Develop in, conjunction with NASA personnel, an appropriate protocol for the application of the procedure under the operational conditions of Shuttle/Spacelab.

SECTION II

ACTIVITY SUMMATION

The initial effort expended on the contract was concerned with Biostereometrics Laboratory installation, survey of automation techniques, and participation in the 28-day Bedrest Study.

Relocation of the Biostereometrics Laboratory from Building 37 to the off-site Technology Incorporated facility was completed by the end of the first month with the exception of the Wild plotter and stereometric cameras along with the keypunch machine. After accomplishing this, the major obstacle to a fully functioning biostereometrics laboratory was the lack of a precise camera aligning system. Full body biostereometric measurement using two sets of stereometric cameras required that the set of points plotted from one stereo pair be in the same coordinate system as the points from the other stereo pair. One method of carrying this out was to level the plotter to a common set of three points for both front and back stereo pairs. The Wild A-40 plotter was not capable of being leveled which necessitated the aligning of one set of stereo cameras to the opposing stereo cameras. The method being used was to mount a telescopic rifle sight on a set of stereo cameras and a mirror on the other set. By aligning the cameras such that the reflection image can be seen centered in the cross hairs of the scope, the two camera sets are very closely aligned. Design and fabrication procedures for this system were initiated.

Involvement in the 28-day Bedrest Study by the laboratory drew to a close with the submission of a draft of the final report to the Baylor Biostereometrics

Laboratory for concurrence prior to its submission in final form to Dr. Phillip Johnson. The physiological response of the six subjects to the extended bed-rest was in many ways similar to the response seen in the Skylab missions.

Since a primary task of the newly established Technology Incorporated Biostereometrics Laboratory was to explore procedures which would lead to the automation of the stereoplotting process. A visit was made to the University of Texas at Dallas and the Jet Propulsion Laboratory in Pasadena, California. Contact was made with Dr. Henry Fuchs at UTD who is exploring a very straight-forward approach for obtaining three-dimensional information directly from the object being measured and who is also researching methods of graphically reconstructing a surface from three-dimensional coordinate data. At JPL Dr. Donald Lynn explained the developing a semi-automatic process for measuring the Martian surface from both long and short range stereo images. Dr. Donald Williams explained the development of a robot vehicle capable of navigating the Martian surface as it selects rock samples and how technological spin-offs from this work could be helpful to automation in biostereometrics. Various considerations and approaches to the overall automation effort were discussed with Dr. Ken Castelman who has considerable experience in three-dimensional image processing.

Measurement in three-dimensions using non-optical linear detectors

A device for obtaining a three coordinate description directly from an object is undergoing research at UTD. The advantages of such a device lies in the utter simplicity of its design. It uses three linear detectors each of which is sensitive respectively to the X, Y or Z component of the location of a

point. By directing a small spot of light onto an object, the coordinates of that illuminated point are directly obtained. And by scanning the surface with this spot of light a mathematical description of the surface can be obtained. The detectors use no lenses and are thus not subject to optical distortions. Development of this device was determined to be at a relatively primative stage at this point in time.

Surface reconstruction using triangles

A computer program has been developed by Henry Fuchs and associates which generates an optimum set of triangles from points lying on parallel planar surfaces. These triangles can then be used to provide a view of an object as it would realistically appear from any chosen angle. Additionally this method of triangular segmentation can be used in calculating volume and surface area of the human body, making it ideally suited for use in biostereometrics.

Computer processing of digited stereo pairs

A vast amount of energy has been devoted to digital image processing at JPL, particularly for the extraction of depth information from stereo images. These digital image techniques have been used not only for creating surface maps using data from Viking orbiter, but is an integral part of the artificial intelligence package of the robot vehicle for Martian exploektion currently under development.

Various approaches are used in making maps there, none of which have been fully automated. A set of software has been developed which is used to make

contour maps from a stereo pair. The process involves manually selecting tie-points or points common to each other in the stereo images, checking for tie-points mismatches, and finally, product generation, all of which takes five working days. Other more traditional techniques are also used which requires less time.

The fully automated generation of three-dimensional data from two stereo pairs is essential to the robotics program at JPL. At present, two highly linear TV cameras produce images from which depth information can be extracted. Although this technique is still under development, it was used to measure a set of selected points from a stereo image pair of a human head. The average error in the 17 points measured was 5.5 mm with a standard deviation of 2.7 mm. A stereo pair of the front and back of a standing subject was left with Bob Cunningham who has done much of the development work in this area. He will slightly modify his software to generate approximately four cross sections, both front and back, from the digitized stereo imagery.

During December 1976 the Technology Incorporated Biostereometrics Laboratory made a large step toward operational status with the arrival of the Wild A-40 stereoplotter and accompanying C-40 stereo cameras from Building 37. The stereoplotter had been given an initial check-out by a Wild Technical representative confirming that no major damage had been inflicted by three recent moves. The instrument received thorough alignment to remove parallax in late February during the factory representative's visit to the Houston area. An engineering oversight in the original installation of the X and Z optical

encoders by the H. Del Foster Company necessitated a modification to the shaft likage between the plotter and the encoders. This minor modification along with the fabrication of the telescopic camera alignment system was accomplished. Planning for the delivery of the keypunch along with the completed construction of the laboratory workbenches and photographic processing sink was accomplished. The Technology Incorporated Biostereometric Laboratory in December of 1976 scheduled to be capable of handling routine full body volume measurements with no help from the Baylor Laboratory by March 1, 1977.

The University of Texas at Dallas - Jet Propulsion Laboratory trip made in November provided a firsthand view of some of the most recent developments in the field of automatic image correlation. The work being done at JPL in the Robotics Laboratory could very well provide much of the technology needed to automate the plotting for biostereometrics. Two sets of stereo plates were left there for a pilot run using their system. Particular interest has been placed in the amount of time required for the run and accuracy of the results.

A thorough search of the literature by the laboratory for information relating to developments in the area of digital image correlation was accomplished. A tremendous amount of work was done in this area although no viable automated system capable of meeting the laboratory's standards appeared to be in existence at that time.

In January 1977, progress toward a fully functioning biostereometrics laboratory continued with the arrival of the specially modified keypunch from Building 37

and redesign work simplifying the optical camera alignment system design. The keypunch machine was reconnected to the X Y Z digitizer with a subsequent test showing all was working well with the interface. Design of the optical camera alignment system had evolved through several different proposed ideas to a simple arrangement which proved to be easy to fabricate and use. Several additional items remained to be resolved before the laboratory could function on a routine basis. These include the acquisition of a set of standard weights for periodic calibration of the weighing platform, modification of the X and Z optical encoder linkage shafts to accept a flexible portion into each shaft, and removal of parallax in the A-40 stereoplotter by a Wild technician.

Investigation into automation techniques continued with contacts being made with persons involved in the Defense Mapping Agency (DMA), Ft. Belvoir Virginia automation effort which is committed to the approach utilizing the manipulation of digitized stereo images. Mr. Crombie with DMA explained the necessity of developing a completely automatic mapping system capable of producing a three-dimensional map totally from digitized image data as received from satellite. Reference was made to the work Control Data Corporation out of Minneapolis, has done supporting DMA's automation goals, which led to an informative talk with Mr. Dale Panton of CDC. All of the information obtained indicated that automation using the digitization of stereo-image densities for subsequent computer correlation appear to be feasible.

However, due to the unique requirements and assets inherent in the close range imagery as found in biostereometric measurement, it was not be possible to

determine, until developmental work got underway, answers to questions relating to expected computer production costs, accuracy of three-dimensional output data, length of time required to develop such a system, and overall stability of this automatic system. Three sizable advantages associated with automation in biostereometrics not enjoyed with terrestrial images are; 1) the basic shape of the imagery under study is constant, 2) a computer recognizable pattern can be projected onto the subject, and 3) the Wild C-40 cameras being used by this laboratory produce images which will require correlation searches only along a line rather than in a designated two-dimensional space and thereby significantly reducing computer time.

In a cooperative effort with the Earth observation division investigation into the feasibility of using the Bendix AS-11B analytical stereoplotter as a practical means to automate the stereoplotting was explored.

In February 1977 efforts continued to align the Wild plotter and camera systems to allow accurately registered stereo pairs to be produced for analysis. The Wild technician had problems with this alignment. The alignment was critical to the accuracy of the total system. An unaligned stereo pair yields grossly or subtly inaccurate results.

Literature reviews revealed several pertinent articles. There were however very few new and innovative things being done in the area of automated biostereometrics or photogrammetry. The literature search continued and contacts with the JPL and Earth resources group were made.

The Wild technician completed the alignment of the plotter and camera system and the laboratory was ready for productive work. There remained only a number of small detailed items to be taken care of.

Time was spent investigating the idea of flying a biostereometric experiment on Spacelab 1. Data from such an experiment could lead to follow-on investigations. The most promising of which would be the development of an Operational Test Requirement (OTR) type device. The development of such a device and its ultimate inclusion in Life Ssciences CORE equipment would allow other investigators to utilize a biostereometric protocol in their other investigations. These additional measurements along with some form of mass measurement could lead to answers about man's early adaptation to Zero-G exposure. Perhaps the initial period of motion sickness could be correlated to cerebral fluid shifts and preventative measures developed.

A CORE photogrammetric technique could also be use to monitor plant and/or fungus growth patterns. It could also be used by materials scientists to better understand crystal growth patterns.

Efforts continued at increasing the accuracy and precision of the biostereometrics technique bringing several new approaches to light. Because of the relative imprecision of the plotting technique, the intrinsic variance of the volumetric measurement is so great that only gross changes and trends can be detected. A large source of this systematic variance can be attributed to the human operator of the scanner. The reproducibility of the scanned result of

a set of stereo pairs is far from excellent, even with the same operator. Once the technique is automated, the human operator will be removed from the loop and hopefully the systematic variance will be reduced to an acceptable level.

Another common technique for variance reduction is to average a noisy signal to allow the signal to enhance while the noise self cancels. If a dual cine technique were developed to take a sequence of synchronized stereo pairs could be averaged to produce a set of measurements with demonstrably lower variance. Such a cine technique could also be used to track breathing and to validate maximum inspiration and expiration. The problem with the development of a cine technique are myriad. The film would have to move between optically flat glass plates with etched fiducial marks. Alignment and synchronization would also be a problem.

The critical requirement for the practical application of such a technique depended on automation of the digitizing and scanning process. To reduce the quantity of data produced by a cine technique by the existing available hard scanning method would be excessive in cost.

Another data gathering technique considered is to use four matched stereo T.V. cameras with common drive circuitry. These cameras produce four outputs corresponding to the two stereo pairs produced by the current photographic technique. With digital methods the T.V. outputs can be directly stored on mass storage as a series of X and Y coordinates and brightness values. These data then can be fed directly into pattern recognition software. The problem of rotational and translational corrections can then be fed into the

software. This work has been under research by the Defense Mapping Agency for some time now and can certainly be treated properly in this simple case.

The other problem of image orthrion linearity and consistency must be more fully addressed before this technique can be implemented.

The problem of automatic analysis of biostereometric photograph pairs or video pairs can be broken into a series of steps. The first is acquisition of the image (photo or T.V.). At this point, the process splits into one of two paths; either digitize then recognize or recognize then digitize. Finally the volumetric computations are performed. These two divergent pathways are discussed.

In the former case the whole of each image is converted to digital form. This form is in essence an X, Y-plane ordered array of measures of density of the negative. Given an eight bit measure of density and a 10 cm x 10 cm negative, if one measurement is taken every 0.2 mm, then an image can be represented as one quarter million bytes or a set of stereo pairs would occupy one megabyte. This is a considerable quantity of data and should be processed by an array processor such as the STARAN processor or by a Cray computer. The result is that the data can be acquired and digitized quickly but the analysis will be a long batch job on a rather large computer.

The alternative is to more nearly duplicate what is being done by hand at the present. That is, locate a point, then digitize it. This could be accomplished

by using a "smart" computer controlled optical digitizer. This special purpose hardware system would locate in parallel common points on each photograph and then digitize it. This would allow for a much smaller data set to describe the image. The cost of the special purpose digitizer might be out of range for a reasonable study.

In July 1977, the Biostereometrics Laboratory was informed that the support of the selection of astronaut/mission specialist candidates would be required. Pictures would be made of archvial quality to support future suit design and physiological parameters such as body componitorial shifts as a function of activity or stress. Suits must be optimized as are conditions to overcome the physiological limitations of man in space. To support the candidate selection, a facility was chosen in Building 7A, Room 342. The area was cleaned and cameras were optimized. Prior to this, a precise camera aligning system was obtained by use of a Redfield 4x rifle scope and traget grids. Precise machining of the supports for the scope and reflectance mirror was accomplished, for full body biostereometric measurements using two sets of stereonatic cameras requires that the set of points (fiducial marks) from one stereo pair be in the same coordinate system as the points from the other pair of stereos cameras.

Inaddition to enable future plotting using the photometric densitometry system located in Building 8 to plot the negatives, various known density/opacity paper stocks were exposed simultaneous with the subject. Metallographic plates were utilized for the negative imaging system.

The Laboratory supported the selection of candidates for astronauts/mission specialists in the Shuttle Program. This was done under the auspices of the M070 experimental series on Musculo-Skeletal function. Using metallographic film which is superior to Tri-pan x for automated plotting techniques, exposures were made of 39 subjects negatives revealed that a micro switch in camera 2 of one of the Wild A-40 stereo pair was inoperable and was promptly repaired. One subject was not photographed due to battery packs. Analyses of the negatives by consultants revealed that the negatives were of superior quality to the negatives from ASTP and Skylab; and past Bedrest Studies. Preliminary attempts of digitizing the images using the automated densitometry system were unsuccessful. A software improvement is required prior to development of this technique. Full-body biostereometric measurements, if this procedure is finalized with the software development, will be available every four hours of machine time, but only thirty minutes of operation time, freeing the biostereometric technician for other functions. The densiometric system is similar and the software may be adaptable to the Defense Mapping Agency developed software.

The Biostereometrics Laboratory continued to support Dr. William Thornton's testing of Astronaut/Mission Specialists in the Shuttle Program. The photographic equipment experienced some problems but was maintained and kept operable throughout the period resulting in the acquisition of negatives which continue to be of better quality than those obtained from ASTP and Skylab. Considerable time was involved in supporting this effort due to the number of candidates photographed and to the schedule to which the candidates had to adhere while they were at the Johnson Space Center.

Work also continued on the software package required to support utilization of the Densitometry System in the Photo laboratory in Building 8. This system automatically digitize the images. This approach, automation based on density of the pictures, is a tremendous savings in time for the Biostereometric technician. Comparisons to software packages available from the Defense Mapping Agency were made to determine if they, with modification, might be adaptable to our needs. It is still too early to make predictions on their applicability.

Dr. Thornton, in addition to being supported as described above, was provided the services of a data technician to assist in the tabulation and plotting of testing data obtained.

In this same time frame, preliminary discussions were held with NASA personnel on the subject of Musculo-Skeletal Research in the coming Space Shuttle Flight Program. The significance of this research is fully understood and it was anticipated that further action would be taken to plan and implement a Musculo-Skeletal Laboratory to support flight experimentation and to define and develop the flight hardware. In view of these requirements, work scheduled for the future would not only include the continued pursuit of automation approaches and for the handling of Biostereometric Data and the tabulation and plotting of information from Astronaut/Mission Specialist Testing, but also the survey of needs for increased Musculo-Skeletal research.

Data Technician Support for Dr. Thornton in tabulating and plotting information from Astronaut/Mission specialist testing continued. The actual photographic

work, however, was completed. The equipment was removed from the laboratory in Building 7A and returned to the Biostereometrics laboratory in the Life Sciences Facility, Clear Lake City. The photographic data obtained during this testing program was reviewed and determined to be of archival quality. Dr. Thornton was pleased with this data bank which will become very valuable both in the pre and post selection time frame. As time goes by, it will serve as a baseline for those candidates selected in their future years with the program.

In the planning aspects of Musculo-Skeletal Research Instrumentation requirements, meetings were held with Dr. Max Anliker, Director, Institute for Biomedizinische Technik, Zurich, Switzerland, and members of his technical staff. Of particular interest was the Densitom II System developed by the Institute. Discussions included both the technical specifications of the system, its application to the NASA's research programs, availability, and cost.

Musculo-Skeletal Research effected by the bedrest mode was discussed with NASA technical personnel specifically on the application of Biostereometric and Densitometric techniques. At that time, in looking at the planned bedrest studies to start in the Spring of 1978, it was agreed that the availability of advanced instrumentation would be advantageous. In the case of the Densitom II System, it was agreed that the institute in Zurich should be negotiated with for their laboratory production unit number two scheduled to be available in a time frame commensurate with the bedrest study need.

State of The Art Computer Automation techniques for imaging were researched through information retrieval systems at the Johnson Space Center and through independent sources. Meetings were held with Biostereometrics program personnel and company computer and engineering groups for feasibility studies of candidate techniques. Digitizing techniques developed and used by the institute in Zurich were received and submitted to these personnel for review.

Dr. Max Anliker, Director of the Biomedical Technical Institute in Zurich, Switzerland advised that the Densitom II System, Number 2, could be completed, tested, and shipped to the United States in February 1978 to meet the requirement of the March scheduled bedrest studies usage. It was agreed by NASA management that Technology Incorporated should negotiate purchase of the system with Dr. Anliker, contractual paperwork for the funding and purchase authorization including "Buy Foreign" was initiated.

With the above decision, detailed specifications of the system along with study reports of previous usage were requested and received from Dr. Anliker. This information was disseminated to computer and systems engineering personnel for review and comment. It was considered appropriate, for maximum utilization of the system, to consider trying to effect a 12 month fellowship for one of Dr. Anliker's NASA personnel in the first year's use.

Technical personnel conducted a comparison study of digitizing and imagine techniques employed in the United States with information received from Dr. Anliker. The study also surveyed system components utilized with the techniques, where they are manufactured, and their performance specifications in relation to known state-of-the-art.

Further planning discussions were held on Musculo-Skeletal investigations for the Space Shuttle Program. The establishment of a centralized laboratory for incorporating Biostereometric, Densitometric, and other related systems required for ground based studies seems, by agreement, to be a requirement. Although not the objective of this contract, our ongoing work by necessity considered these future plans and many of our decisions, with NASA approval, were made with this in mind. Automation and system development for specific adaptation to space flight requirements still held priority position in our thinking.

At this time, future plans included finalization of the acquisition of the Densitom II System, further familiarization of its specifications and operating procedures, interface requirements with data systems currently at the Johnson Space Center or in industry facilities under contract to the NASA, and Biostereometric and Densitometric applications for bedrest studies. Also, software requirements for automation on acquisition, interpretation, and display were continued to be studied and their potential utilization examined for determining those most feasible to employ.

The Director of the Biomedical Institute, Zurich, Switzerland, visited our biostereometric laboratory. Discussions were held on the Densitom II Systems technical capability, its inherent data acquisition and handling characteristics, and the enhancement of these characteristics by interfacing into the Johnson Space Center's computer banks. In addition, the status of the development schedule and its availability for shipment to the United States was reviewed.

Having obtained the proper contractual approval in advance of Dr. Anliker's visit, a purchase order was issued to him for the system with a ship date of February 25, 1978. Discussions were held on the subject of providing engineering support from his shop for setup, checkout, and training. No decisions were made as this was not a responsibility of the contract. An approach to an agreement on the software package required for the Densitom II was agreed on.

A lot of discussion in this report has now reflected activity in Densitometry as well as Biostereometry. The two areas, the measuring of density and the measuring of volumes, are interrelated and are essential to investigative research on Musculo-Skeletal changes predictative of those that will occur during long periods of weightlessness, or investigation of these changes by periodic measurement during actual spaceflight.

Imaging techniques, a rapidly changing and progressive technology, are vital to both measurements. As we pursue one, we learn about handling the other, automation, our key and number one responsibility, is vital for in the case of Biostereometrics, the handplotting approach to finalization of data is totally inefficient and time delaying. The possibilities are numerous from the various data formats available for the computer but there are inherent problems with any simple selection.

Two aspects were carefully considered, (1) Do not take an approach to recreate the wheel, this is too costly and time consuming, (2) Select candidate programs which have the greatest potential for successful utilization with minimum

cost and time involved for rewrite modification. Our efforts carefully considered both. It is deemed better to evaluate a program or approach and after having done so, discard it (when determined to have too many weaknessess) rather than proceed with one for the sake of having made a selection.

After the Director of the Biomedical Institute, Zurich, Switzerland, Dr. Anliker, had visited the Biostereometric Laboratory and a purchase order had been issued for a Densitom II, interfacing of the two groups was accomplished by communications concerning technical aspects. The Biostereometric Laboratory technical staff was able to provide answers on questions concerning hardware, software, and the type and availability of test equipment required to support the proposed effort. An areas was cleaned and set aside in the laboratory for the instrument which is expected to arrive before February 25, 1978. To furnish a source of 1125 for the instrument, a request was made to the NASA-JSC Radiological Health Group for approval to buy one 500 m Ci source for the instrument. No approval was granted for NASA-JSC AEC licensing will not tolerate the source. A letter was then submitted to get the source on Texas Regulatory Commission license 8-8927.

To further enhance man's knowledge of volume changes in his body due to weightlessness, support was given to Flight Medicine in instereoplotting of the circle of Willis and associative blood vessels in patients which have received angiograms. Three dimensional plots of the blood vessels were obtained and potential leisons noted. Positional effects as could be related to space flight maneuvers were noted. It is emphasized that this data is only preliminary on a few patients.

The addition of the Low Body Counter (K^{40}) facility to the densitometry and biostereometrics aspects of measuring density and fluid shifts, respectively, greatly improved the investigative research on Musculo-Skeletal changes predictative of those that will occur during long periods of weightlessness, or investigation of these changes by periodic measurement during actual spaceflight. This facility was added during the month of February, 1978.

In preparation for the arrival of the Densitom II, effort was expended to receive the necessary licensing for an instrument which uses radiation in its detection sequencing. A preliminary site inspection was held by the Radiation Health and Safety Group of the Texas Department of Health Resources. Approval was then given for the next step in the licensing sequence, which is an on-site inspection of the machine and then a review of proposed radiation safety and isotope handling and storage procedures. A copy of the license with the approval amendment for that particular source was submitted to the manufacturer who delivered the source within four weeks.

Minimal support of the stereoplotting of the angiogram visualized blood vessels was given to Flight Medicine to complete the preliminary study as to the feasibility of stereoplotting of x-ray imaged transparencies. These pictures were not of the quality experienced in the stereophotogrammetry of the Biostereometrics Laboratory.

Work continued on the modification of the camera supported targeted range-finding system to measure camera distance, height, and projection. The

modification enables measurement of cameras without the tedious measurements of height and distance, taking and developing of images, and the repositioning of the cameras based on this interpretation. This modification removes the aspect from the trial and error stage to a more exacting relationship. Ease of camera adjustment is essential to the potential of biostereometrics in space flight.

Work on the Low Body Counter (K^{40}) facility area began by assignment of an individual to test, repair, and/or update the facility on an as-needed basis. The facility would then be available for use by the Life Sciences Division investigations to support various research investigations, especially in the area of Musculo-Skeletal function where it would complement the expected Densitom II and Biostereometrics Laboratory. A testing protocol as to the efficacy of the radon scrub was planned to submitted upon the completion of bringing the facility on-line.

Further efforts were expanded on the target imaging system modification by having several parts machined to developed drawings.

A new individual was added to the staff to develop a program in osteofracture measurement techniques. This had important ramifications as to the spaceflight induced osteoporotic effects in weight bearing bones. A procedure was developed to monitor the bone healing by the Densitom II when it finishes the USPHS - San Francisco Bedrest Study and x-ray imaging techniques. Quantitation of repair rates by tetracycline labelling techniques were under further developed.

The Densitom II was shipped from Zurich, Switzerland, via air freight to Houston, Texas. However, due to problems encountered by the customs people, the Densitom II was not released from customs. This affected the isotope source licensing arrangement as the Texas Department of Health Resources was not able to inspect the machine and make their recommendations. A waiver to this was requested. However, the earliest that the I^{125} source could be obtained was approximately June 15, 1978. It was feared that this might impact the transhipment to USPHS - San Franciso for the July 4, 1978 Bedrest Study Start-up date. The problem was solved however and the schedule adhered to.

A new doctoral graduate of Dr. Anliker arrived from the Institute of Biomedicine to train personnel in the use of the Densitom II and to modify the software where necessary. Due to the unavailability of the Densitom II, he worked on the PDP 11 in Building 37 where he developed and modified existing software for enhanced image analysis. His effort continued until the Densitom II arrived.

Work on the LBM (K^{40}) facility was continued with system checkout proceding on a systematic basis. Samples of KCL were obtained, verified, and boxed for the making of dummy body compositional measurement and instrumental standardization. Checkout of the facility computational hardware proceeded.

The osteofracture analyst developed a technique for minimal blood loss by simulated breakage of the femur in rats by drilling. A bone shear was found to be entirely too severe and resulted in a fracture that followed stress indices. Drilling was much less severe. Size of drill, pressure, and other similar questions remained to be answered.

The Densitom II was released from customs and placed in the Biostereometrics Laboratory. Checkout of the hardware revealed that several connections were inadequately joined and had separated in transit. Trouble shooting detected these and resulted in repair. In addition, I^{125} source was procured with delivery expected in June. This was accomplished by waiver from the Radiation Health and Safety Group. Software modifications developed on the PDP 11 were tested and remodified as required. These modifications improved the precision and accuracy to $\gtrsim$ 99.5% on the phantom. Modifications continued to improve the precision and accuracy. A modification of the software program was made to enable the study of the rate of healing in rat bones. The program modification enabled the imaging and quantitative of the bone and hole in the rat femur. This was scheduled to be used in conjunction with the osteofracture protocol.

Checkout of the K^{40} facility was continued with software loading of the hardware being the primary endeavor. Problems were encountered in the optical reading unit of the paper tape reading system. An individual from the facility attended an international meeting in Toronto on the use of computers to monitor body composition.

Leisons producted to monitor osteofractures were developed to the point of relative uniformity. Drilling rate and bit size were standardized to give a comparison size and with no tissue injury due to heating of the tissue. X-ray of the bone has shown fairly consistent healing rate.

Work on the Densitom II continued. A new I^{125} source was received just prior to shipping the instrument to USPHS - San Francisco. It was installed in the instrument, various tests on leisons of bone was conducted. Imaging of the bone was precisely defined on a bone which had not been excised with one which had. This phase work was planned to be continued upon return of the Densitom II from the USPHS - San Francisco Bedrest Study.

Work on the osteofractive study was co-ordinated with that of the Densitom II. Techniques were refined as previously discussed. To further develop the investigational performance of the study, meetings were held with researchers from Baylor College of Medicine and Methodist Hospital. Proposed areas of future studies involving also neutron activation and differential tetracycline label of bone tissue were discussed. A proposal to further study bone healing in space flight using developed techniques and these suggested areas was submitted in response to the Announcement of Opportunity (AO).

In an effort to further explain the body compositional changes in response to space flight, a hydrostatic weighing facility was visited and preliminary plans for developing such a system proposed. This will be utilized to support the biostereometric evaluations.

The Densitom II was received at USPHS - San Francisco prior to the start of the Bedrest Study. Hospital personnel unpacked the instrument and assembled it despite posted printed and telecommunicated warnings against such an occurrence. Upon arrival of laboratory personnel, several of the electronic circuits had to be repaired, which delayed start of the instrument use. Similarly, inadvertant radiation exposure occurred to one of the hospital employees, which could have had serious consequences. Set-up and use of the machine through use of the University of San Francisco PDP 11 to modify software was accomplished.

Work on the osteofracture study preliminary efforts were continued. The majority of the laboratory effort was expended to get the Densitom II operational for the USPHS - San Francisco Bedrest Study.

Support of the USPHS - San Francisco Bedrest Study preliminary subject (Pre-bed phase) was conducted and calibration data for each subject obtained. USPHS - San Francisco hospital employees assisted in modifying the Densitom II for making heel scans and tibia measurements. The modification will enable direct comparison with the Norland Cameron Rectilinear scanner. This work will continue for seventeen weeks starting in September. Computational support of the data and systems software designs modifications was accomplished by laboratory personnel.

An experimental protocol for the monitoring the healing rate in rats of 300 g body size (equivalent to a 35 year old man) was developed and is presently undergoing peer review for scientific and technical merit. Upon receipt of

the approval document, personnel will initiate the proposed plan. This is basically to drill holes in the femur of different sizes, allow to heal while monitoring with x-ray, and to sacrifice at various time intervals post-trauma to monitor by pathological techniques.

Check out of the LBM (K^{40}) facility is proceeded. Testing of the detectors revealed that 4 of the 6 were substandard and were returned to the factory for refurbishment. Random problems with the computer program input system still plagued the software input sequencing.

Support of the USPHS - San Francisco Bedrest Study was continued. Improvements in the Densitom II software system have continued. Work accomplished to this part has improved the system to a 99.7% accuracy and precision. This effort of bedrest support continued until January 1979.

Development of the operational capabilities of the low level body potassium (K^{40}) facility continued. The Nuclear Data ADC system was found to have several electronic abnormalities caused by electrical power surges which must be repaired by the factory prior to continuing tracing system. This effort was worked with the factory representative.

Work is continued on the bone healing study previously outlined with preliminary results being extremely encouraging.

SECTION III

ISOTOM HARDWARE - SOFTWARE SYSTEM

1. Introduction

The work described herein was a very important portion of the contractual obligation. It discusses three different topics.

- minor modifications and occasional repairs of the hardware of the system
- modifications of the Isotom system software and development of an off-line CT evaluation system
- the carrying out of CT-measurements, mainly on bedrest subjects, but also on osteoporosis and dialysis patients, on monkeys and on rats.

After a short introduction in the Isotom hardware-software system a description of the developed modifications is given followed by a documentation of the new off-line system as it was used for the evaluation of the bedrest CT-data. The last part is devoted to a detailed description of the bedrest study, i.e. the measuring procedure, the evaluation of the CT-images and the preliminary results that could be obtained.

2. The Isotom g-CT Scanner

The Isotom g-CT bone scanner is a single beam rotation-translation scanner to be used for CT-measurements on the extremities, i.e. the calcaneus, the tibia (distal only) and one radius. It uses a ^{125}I nucleid as radiation source and highly accurate pulse counting techniques and features therefore high accuracy low dose CT-imaging of the bones. One CT-measurement lasts between five and eight minutes depending on the choosen scan diameter.

The Isotom is comprised as a scanning device for the rotational and translatory movement of the source/detector system, complete with stepping motors, photomultiplier, preamplifier and safety circuits, and an additional hardware cabinet containing the following modules:

- An IBT (acronym for Institut fuer Biomedizinische Technik) scanner interface with a Motorola M6800 microprocessor for the control of the stepping motors and the data transfer from scanner to memory.
- A Texas Instruments TI 990/4 microprocessor for the operating of the system, i.e. the initialization of a CT-measurement, the on-line reconstruction and evaluation of the CT-image and the data transfer to and from floppy disk.
- An IBT floppy disk interface and a dual floppy disk drive for the storage of the CT-data and the initialization of the software system.
- An IBT RAM video display memory with 32 k words display memory, 8 k words overlay memory and 32 k words microprocessor expansion memory.
- Additional hardware, a video monitor, stepping motors power supplies, pulse discriminator etc.

The system is initialized by "power on" which activates a PROM boot strap loader. This loader is a short program that reads the system software from floppy disk into the TI memory in a certain unique relationship, i.e. each sector on the floppy disk corresponds to a certain memory area in the TI memory. After termination of program input the software system starts operating and the Isotom is ready for use. Figure 1 gives a schematical overview of the Isotom hardware configuration.

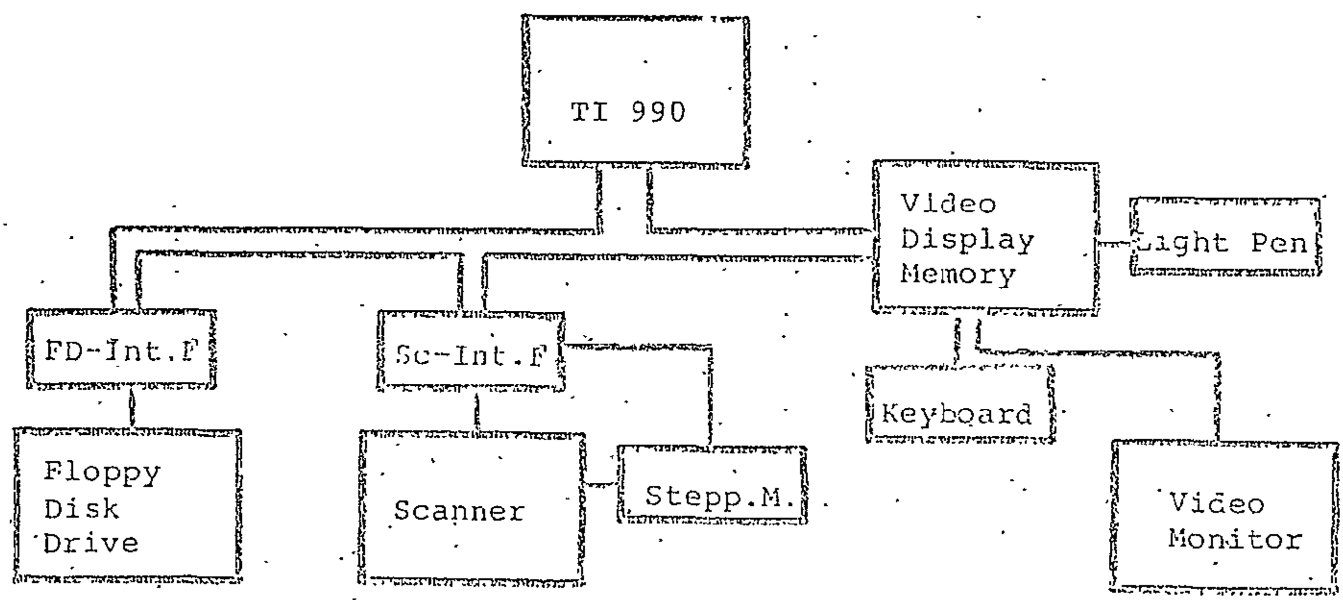


Fig.1: The Isotom hardware configuration

The Isotom software system comprises the following modules:

- A module for the on-line reconstruction of the CT-images
- A module for the evaluation of the reconstructed CT-image
- A module for the control of floppy disk input-output
- A module for the expansion of the CT-image (the reconstructed CT-image is a matrix of 128x128 words while the expanded image is a 256x256 byte matrix)
- A main module for the control of the program sequences

The interrelation of the different program modules is given in Figure 2.

3. Modifications on the Isotom CT system

The Isotom g-CT-scanner is the prototype of a new generation of microprocessor operated low cost scanners. It is quite clear that such a prototype is not free from some small deficiences that appear only during extensive and practical use of the device. Moreover, the use of the Isotom for the observation of long term bone mineral loss has no precedent, neither was it ever used for series measurements on the tibia and the calcaneus. Therefore, it was expected that some small changes of the hardware might prove to be necessary. This eventually became a reality. Also, we knew that the construction of the holders for measurements on the tibia and the calcaneus would not be straightforward - indeed a good part of the base line period (see 6.1) (in the case of the tibia holder even too large a part) was used for the development of these holders. The following gives a short documentation of the hardware-software modifications of the Isotom system that proved to be necessary or desirable.

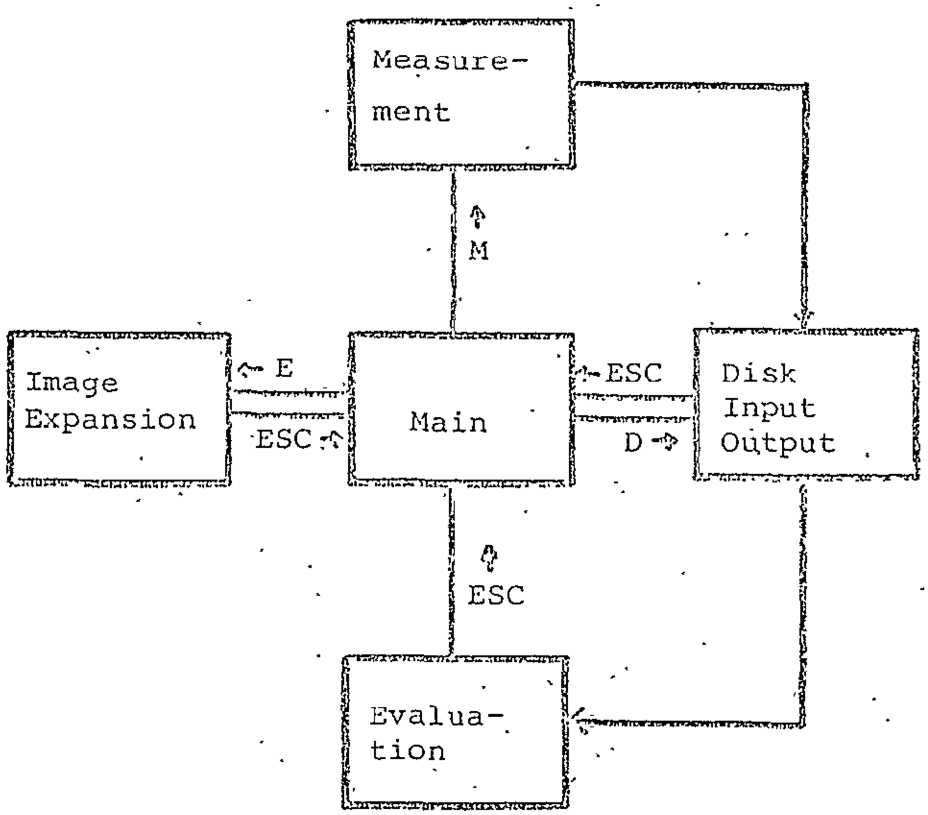


Fig.2: The Isotom software configuration

3.1 Hardware Modifications

The floppy disk drives had to be modified to be compatible to the 60 hz frequency of the U.S.A. as it was originally designed for a 50 hz line frequency. This was achieved by a mechanical reduction of the gear ratio of the two disk drives by 16 2/3 %.

- The noise level on the signal path, induced by the stepping motors feeding current peaks, proved to be intolerably high. This situation was improved by a modification of the wiring of the scanner, consisting in a separate shielded 20-pole cable from the stepping motors power supply to the stepping motors. In addition to that, the preamplifier gain was changed by a different feedback resistor ratio from 20 to 5. This gain loss was compensated by higher photomultiplier acceleration voltage (1340 V). The combined effect of those three measures resulted in a vastly improved S/N ratio. The pulse height spectrum of Figure 3 shows the excellent response of the counting system. The remaining measured background (0.15 p/sec) can be assumed to be entirely due to natural background radiation. The theoretical S/N ratio is readily computed to be over 110 dB.
- The first extensive test of the CT-scanner at the USPHS Hospital, San Francisco, California showed a dependence of the reconstructed bone parameters on the position of the object to be measured in the scanner opening. Part of this problem is due to the software evaluation (see 3.2), but the main effect proved to be induced by the specific collimator system that was used. This system consisted of a round source collimator opening (diam. 1 mm) and a rectangular detector collimator opening of 5 by 1.5 mm. This configuration was choosen to

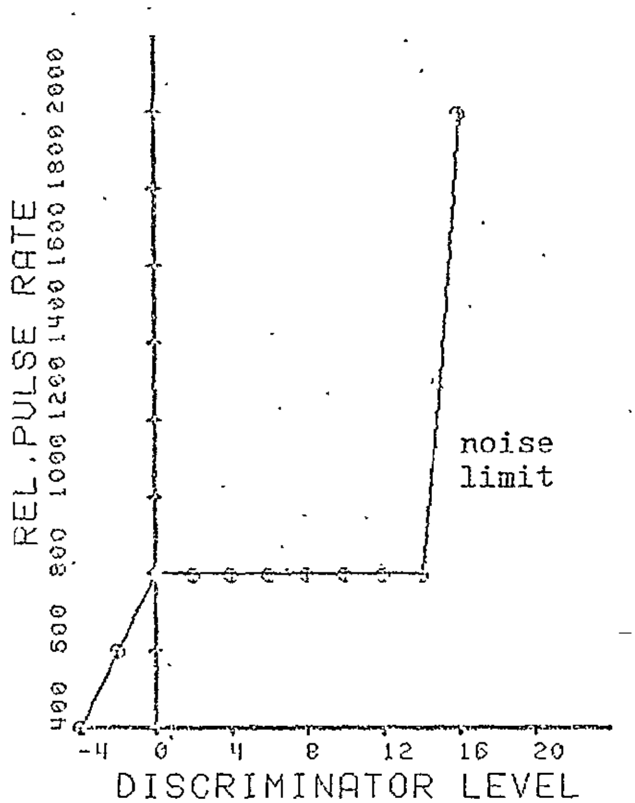


Fig. 3: Integral pulse height spectrum

assure a minimal irradiation of the patient with a maximal exploitation of the information content of the transmitted photons. However, it has two severe disadvantages:

- The use of a conical measuring beam (see Figure 4) entails the aforementioned position dependence.
- The geometrical resolution (and therefore the precision) is reduced, mainly in axial direction.

These negative effects proved to be too high for longitudinal studies. Therefore, a different collimator system was used, consisting of a source and of a detector collimator with circular openings of 1.5 mm diameter each. This configuration increased the patient dose by a factor 2.25. However, in view of the still very small dose (ca. 10 mrem) and the appreciable increase in precision this measure was felt to be justifiable.

- In anticipation of necessary calibration measurements (see 4.5) a switch was installed in the front panel of the stepping motors power supply which allowed for the discontinuation of the rotational movement of the source-detector system.
- The main fuse holder of the stepping motor power supply was changed to be compatible to U.S. norm fuses.

A major problem was the construction of holders for CT-measurements on the tibia and calcaneus as well as the modification of the holder for measurements on the radius. With the competent help of Dr. Larry Quan who did most of the actual constructing work and by repetitive test

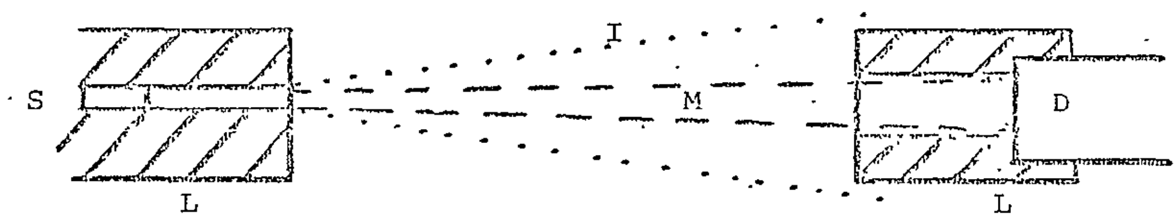


Fig.4: Isotom detector configuration (unmodified).
S ^{125}I source L Lead, D Detector, I irradiation
cone M measuring cone.

measurements on voluntary subjects the holders sketched in Figure 5 were developed. We used the following landmarks as reference points (refer to Figure 5):

Ulna/radius:	The olecranon process of the ulna
Tibia/fibula:	The sole of the foot, i.e. the posterior part of the os calcis, the head of the first metatarsal and the head of the fifth metatarsal
Calcaneus:	The posterior-inferior part of the os calcis

These holders allowed for an estimated repositioning error of ±1 mm. It should be noted, that a repositioning error of this order is still to large for high precision measurements, at least at measuring sites containing mainly cancellous bone (as opposed to compact bone). However, this precision proved to be satisfactory in combination with the later described new area calibration method (See Section 5).

3.2 Software Modifications

The Isotom was delivered as a dedicated microprocessor system with no options allowing for the modification of system software. However, as mentioned in Section 2, there is a unique relationship between program memory area and program disk location, i.e. each sector on the program floppy disk corresponds to a certain microprocessor memory area. This allows for modifications of the system software by changing the machine code instructions of the assembly language commands on the program floppy disk with the aid of an off-line computer (See program KORFLO, App. A)..

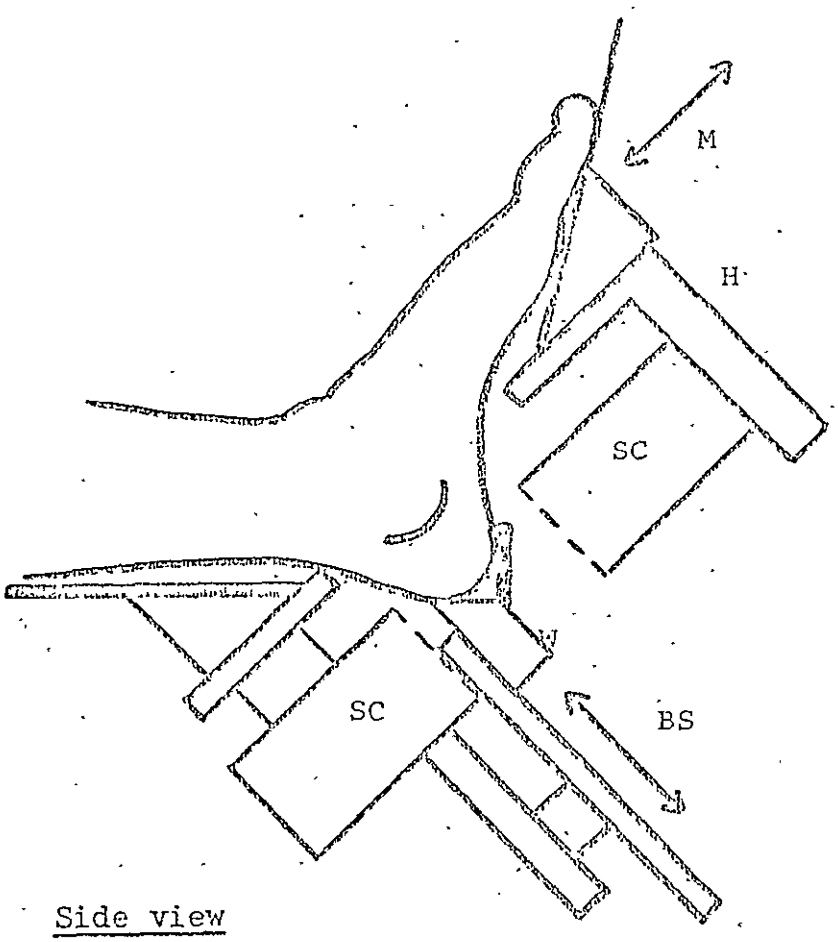
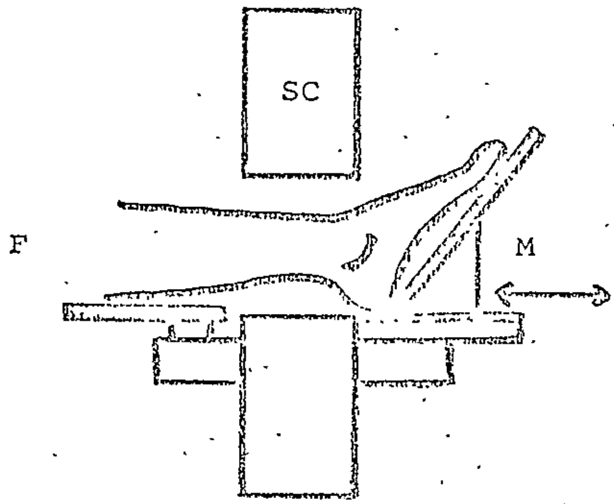
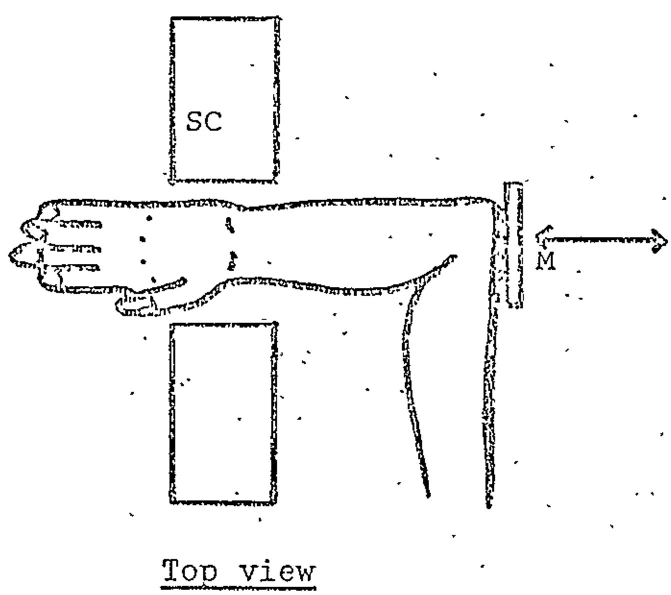


Fig.5a: Holder for CT-measurements on the cal-
caneus. SC Scanner Madjustable part, H Holder
W Wedge, BS Back support



Side view

Fig.5b: Holder for measurements on the tibia. SC Scanner M adjustable wedge, F front of scanner.



Top view

Fig.5c: Holder for measurements on the radius. F fornt of scanner SC Scanner M adjustable part.

Notably, this procedure allows only for small changes in the software as the structure of the original program cannot be altered. A far superior and more comfortable way to do actual software developments would have completed the Isotom hardware in a way that it could have been used as a complete minicomputer. Yet, the purchase of such a keyboard turned out to be impossible for financial reasons.

The above described method was used to arrive at the following modifications (all programs mentioned are off-line programs, developed on a LSI 11 floppy disk minicomputer.

- Studies on mathematical methods showed that 43 projections are only marginally sufficient to reconstruct artifact-free CT-images. Therefore the number of projections was increased to 60 which in turn made a modification of the backprojection tables (as they are used to backproject the filtered projection data across the image matrix) necessary. For the calculation and insertion of these new tables program SINFLO was developed, which also allows for an on-line magnification of the reconstructed image (currently this magnification factor is set to a linear magnification of 1.25). In order to avoid a prolongation of the measuring time, the speed of the stepping motors was increased by about 20%.
- The color look-up table of the video display, which consisted of only 16 different colors, was changed to a cyclic rainbow like color scale

containing 210 different colors, thus arriving at an almost continuous color coding (program COLOR, COMB). See Figure 6.

- The on-line reconstructed image was rotated by 90 degrees in regard to the actual scanned cross-section. This was changed to arrive at correspondingly lying CT-image and cross-section.
- The on-line beam hardening correction tables were changed to values calculated out of plexiglass wedge measurements.
- The smoothing of the input data was omitted, first because it was faulty, secondly because maximal geometric resolution was required.
- A separate Isotom program was prepared for rat measurements. Rat measurements have to be carried out with a geometrical resolution in the order of 0.1 mm, i.e. with a much smaller measuring photon beam and therefore with much lower photon counting rates. To compensate for that, the measuring time has to be increased by a factor of 5 to 10 which was accomplished by running the stepping motors at their lowest possible speed and by increasing the number of projections to 96. The contrast of the reconstructed CT-image had to be increased by a factor of 8.
- The 'expand' module (See 2.2) was modified to display in the lower left corner the date, the measuring site and the patient name.
- An additional routine was inserted into the module 'measurement' (See 2.2) which calculates on-line the distance between left and right bone boundary and the total absorption inside these boundaries for each linear scan. The resulting information is displayed on the video screen after each completed scan. This routine was developed as an additional repositioning help.

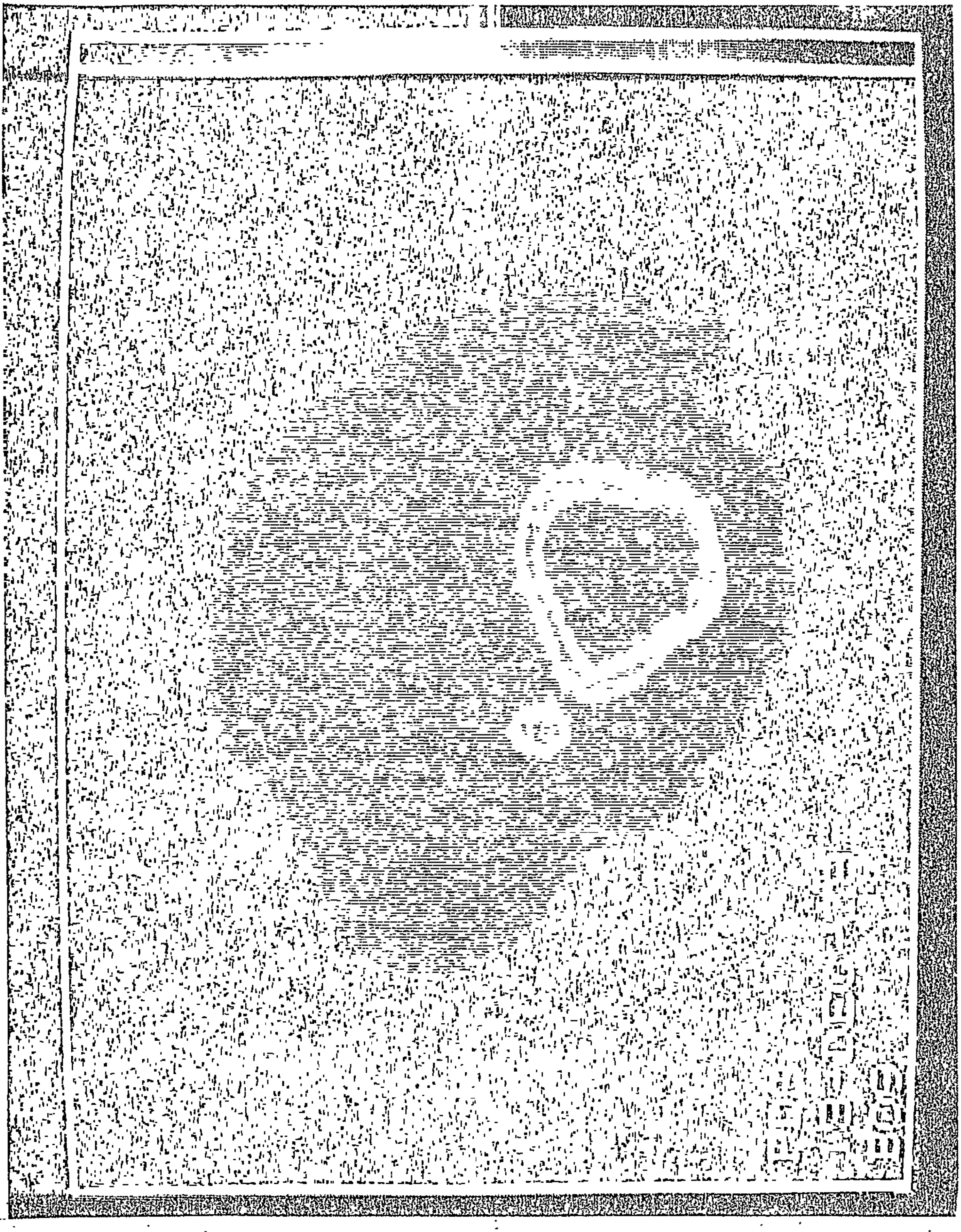


Figure 6: CT-image video color display demonstrating the modified color scale and the identification in the left lower corner of the screen (see text).

4. The CT off-line Software System

4.1 Introduction and Overview

The TI 990/4 microprocessor implemented in the Isotom hardware system has two major restrictions which limit its use for the performance of advanced on-line CT programming techniques:

- It is comparably slow (although faster than most other microprocessors)
- The TI system software (Prototyping or FS operating system) is not yet up to the state of the art.

In order to be able to perform a more accurate and partly different data analysis, a complete software off-line system was developed. This CT-system was developed and run on a LSI 11 DEC minicomputer operated with the RT11 floppy disk resident operating system. It may be run on any DEC computer operated by RT11 and can be either floppy disk, hard disk or DEC-tape resident. The CT system has to perform several functions:

- The data transfer between DEC computer and TI 990/4
- The calibration of the CT-data, i.e. beam hardening, dead time and background correction of the input data and absolute calibration of the reconstructed attenuation values.
- The reconstruction of CT-images.
- The evaluation of CT-images
- Patient data base management
- Several utilities routines, such as fast disk to disk copies, file transfer programs etc.

The CT-system developed along these lines is provided as a package of eight different programs and two information files, all resident on the system device. The interrelation of the individual modules is shown in Figure 7. Table 1 gives an overview of the allocation of the different input-output channels for the three possible system devices:

System booted on:	Isotom floppy disks in drive:	Software resident on:	RT11 data files on:
Dectape	DXo**	DTo**	DT1
Floppy disk	DXo	DXo	DX1
Hard disk	DXo	DKo**	DK1

*   Floppy disk drive
**   DEC tape drive
*** Hard disk drive

Table 1

All interrelated programs in Figure 7 need to be resident on the same device, i.e. all programs except TIPDP and PICTRA. By default the keyboard is used as list device, however, a simple 'assign' command can redirect the listing output to any print only device.

4.2 Functional Description

- TIPDP is used to transfer Isotom CT-data files to RT11 data files and to set the 'empty' flag in the Isotom disk directory.
- CTIMAG and CTIMA are used to reconstruct CT-images using interpolated backprojection techniques. CTIMAG accepts individual filenames while CTIMA searches the whole data device for not reconstructed data files and reconstructs these files sequentially (there are maximal five CT-files on one floppy disk, maximal 50 on a hard disk). Thus, CTIMA

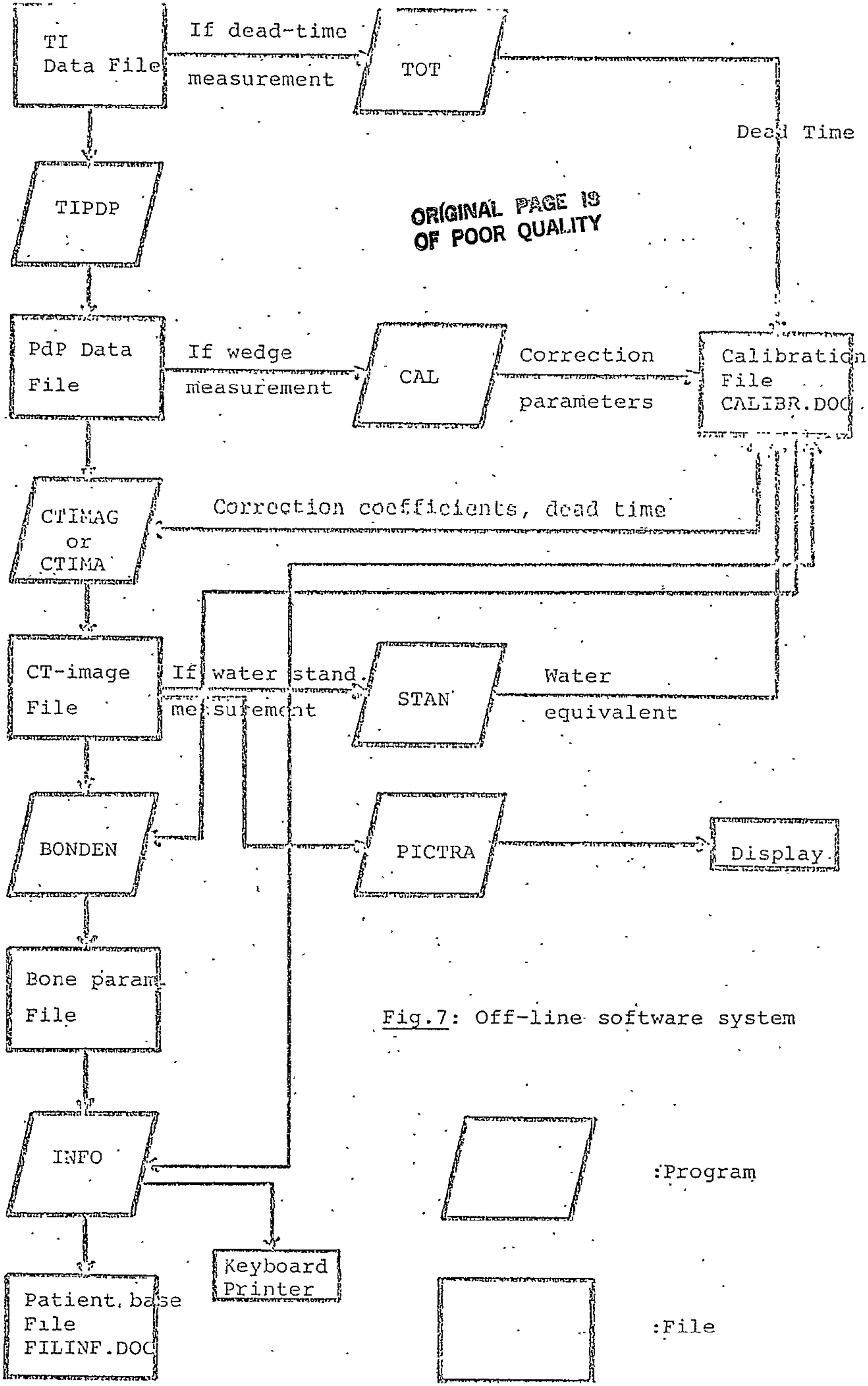


Fig.7: Off-line software system

is useful for series reconstructions of large data volumes without operator assistance.

- BONDEN evaluates the bone densities of the bones present in the CT-image (max. two), converts the computer units to absolute attenuation coefficients and stores the resulting information in the patient data base file FILINF DOC.
- INFO is used to print out patient information from the data base file.
- TOT is used to calculate the dead time of the system
- STAN calculates a water equivalent attenuation coefficient for the conversion from computer units to absolute attenuation coefficients.
- CAL calculates a second order correction function out of a plexiglass wedge measurement to compensate for beam hardening effects (first order compensation).
- PICTRA allows for the transfer of off-line calculated CT-images to the ISOTOM video display.
- DXCOPY performs a fast disk to disk copy for backup purposes.
- PDPTI transfers data from a RTLL file to a Isotom floppy disk. This option allows the testing of the on-line reconstruction with mathematical modell data.

A listing of all these programs and listings of all necessary subroutines not mentioned here is provided in Appendix A.

5. A New Method to solve the Repositioning Problem

The crucial problem of longitudinal bone mineral studies, such as bed rest studies, is the achievement of a high precision. Large repositioning

errors render a high accuracy meaningless and can well devalue an otherwise perfect method. This repositioning problem is doubly serious if one wants to measure at sites where the bone is mainly comprised of trabecular bone, because at such sites one observes always large axial inhomogenities of the bone. Studies on dead bones with the Isotom scanner showed that a repositioning error of 1 mm can cause a difference in the bone density parameter of as much as 4%. However, this problem could be completely solved by taking into account a second important bone parameter. This parameter with precise evaluation procedures can be calculated to a high degree of accuracy, and prove to be a very smooth functional relationship between cross-sectional area and mean bone attenuation coefficient (Figure 8). Therefore, the acquisition of a few strong points on such a curve allows for the interpolation of intermediary values. In other words: A series of four to five adjacent CT-measurements gives a very precise knowledge of the bone mineral distribution between the two CT-images lying furthest apart. Any subsequent measurements on the same patient at the same yields again a mean attenuation and a cross-sectional area and as long as the measuring site is positioned inside the region covered by the calibration curve (typically 3 to 5 mm) this mean attenuation can be compared to the original one with a high degree of precision. This method is valid under the assumption the cross-sectional area of the bone does not change in time - an assumption that seems safe.

A longitudinal bed rest study using this method should be planned in the following way: During the base line period a series of adjacent CT-images should be measured on each patient and for each measuring site

(i.e. radius, tibia and calcaneus). These measurements then yield a series of calibration curves. Later on, for the observation of the bone mineral versus time, only one measurement needs be done on each measuring site and for each time interval. The repositioning facilities have to be good enough to assure a positioning of the patient in a manner that the measured CT-image lies inside the axial region of the respective calibration curve. Suppose now that such a measurement yields a cross-sectional area F_i and a mean bone attenuation m_i. The calibration curve defines a functional relationship between the cross-sectional area F and the mean bone attenuation m_c:

$$m_c = f(F)$$

It follows:

$$m_{ci} = f(F_i)$$

and for the relative bone mineral change R:

$$R = (m_i - m_{ci})/m_{ci}$$

The precision of this parameter R is dependent on two things:

- o Movement artifacts
- o Accuracy of the method

As the accuracy of the Isotom is very high one can say that the precision of this parameter R is only dependent on the largeness of the usually invisibly small movement artifacts.

A quantitative value for the precision of the CT-method can therefore only be given in an approximative way. However, it follows from the base line period of the bedrest study (See Section 6) that the precision is better 0.8%, in some cases even well below 0.5%.

6. The Bedrest Study

6.1 Protocol and Procedures

The NASA long term study which took place in the San Francisco USPHS hospital under the direction of Dr. V. Schneider was planned as a combined study of the calcium metabolism of bedrest subjects. Along with several biochemical methods, CT-g-techniques were used for the first time to check whether this method could yield higher precision values of the bone mineral changes then well established methods, such as the VCH rectilinear scanner. The following protocol was used for this study: Ten weeks base line period, 17 weeks bedrest and four weeks reambulation. A total of three subjects were observed for a complete bedrest term during my stay in San Francisco. We were allowed to measure each subjects every two weeks on the calcaneus, the tibia and the radius. The arrangement of the aforementioned holders had to allow for a lying position of the subjects, as they were not permitted to stand on their feet even for the shortest period. The subjects were therefore measured lying on a gurney - on their back for measurements of the radius. The on-line reconstructed CT-image proved to be indispensable for two reasons:

- to check whether any visible movement artifacts are present in the CT-image

- to check in a qualitative way whether the patient has been correctly positioned

The CT-data of the Isotom was transferred to RT11 data files and stored for later off-line reduction. This off-line treaty of the CT-data was begun as soon as the off-line CT-system was developed.

It should be noted that such off-line evaluations involve high computer times - the off-line reduction of all bedrest data needed an estimated time of more than 90 hours.

6.2 Shortcomings and Pitfalls

- A big problem consisted in the fact that the bedrest study began before any kind of holders for CT-measurements on the tibia and the calcaneus could be designed.
- The repositioning method as it was described was devised at a time well inside the bedrest period. As a consequence of that, the necessary calibration data had to be reconstructed from accidentally mispositioned CT-measurements and is therefore incomplete, marginally sufficient for the calcaneus/radius measurements but insufficient for measurements on the tibia.
- The storage of CT-data on floppy disks is relatively unsafe. About 15% of the data was lost due to disk drive malfunctions and floppy disk formatting errors.
- The observation of only three subjects is not enough to yield any reliable quantitative results.

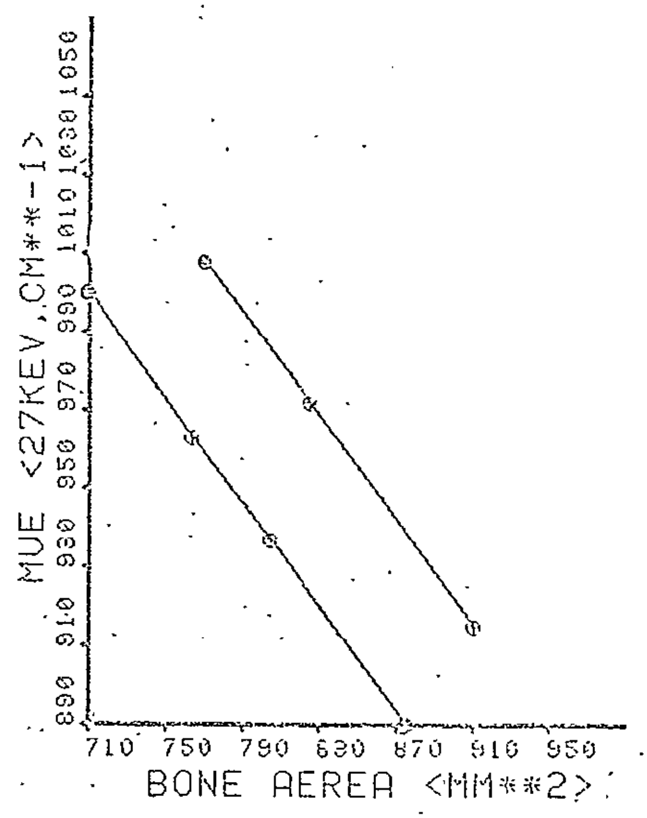


Fig.9: Calibration curves MW. The black points correspond to extrapolated values

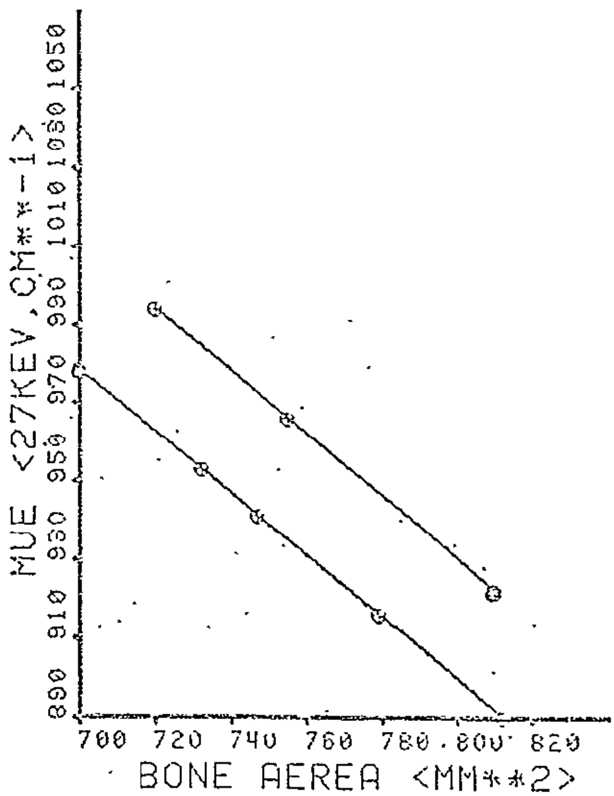


Figure 10: Calibration curves JD.
As in Figure 9.

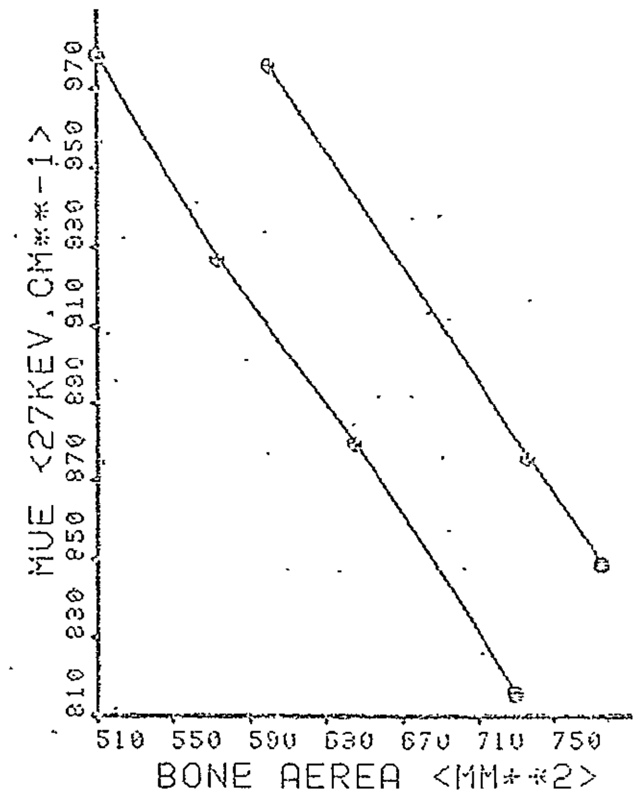


Fig.11: Calibration curves BF

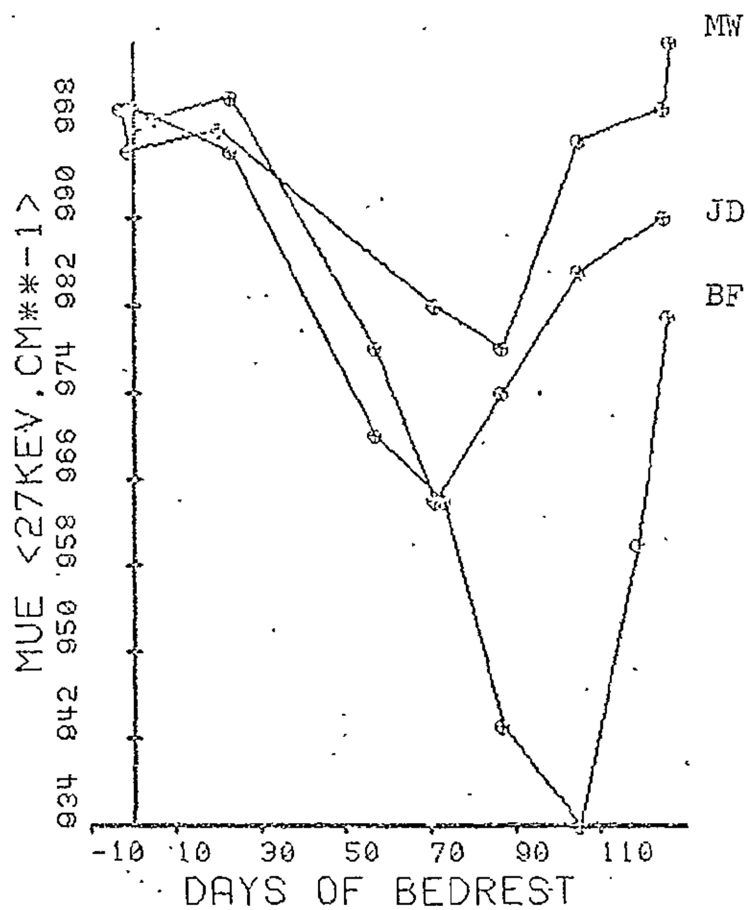


Fig.12: Mean bone attenuation co-efficient relative to the base line mean bone attenuation coefficient as a function of time. Bedrest ends at day 119.

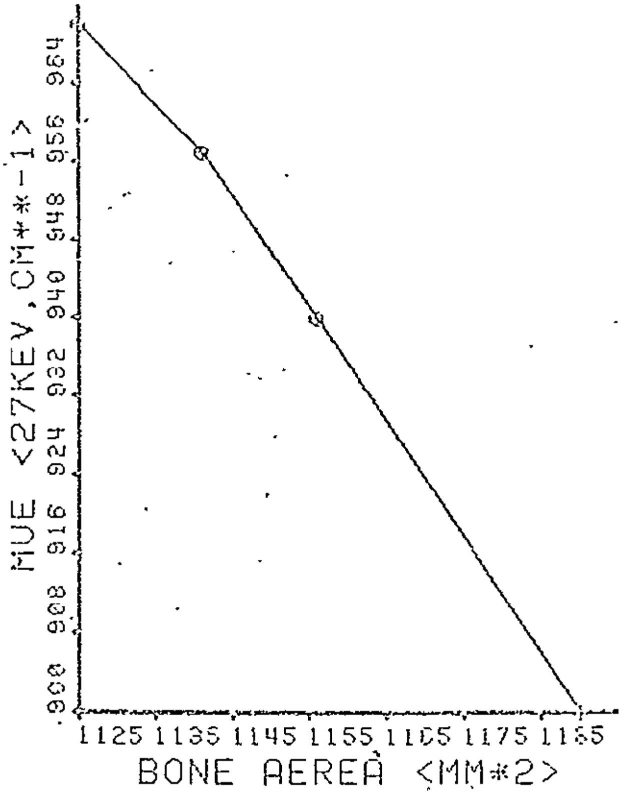


Fig.13: Calibration curves for MW for measurements on the calcaneus. The black points represent extrapolated values.

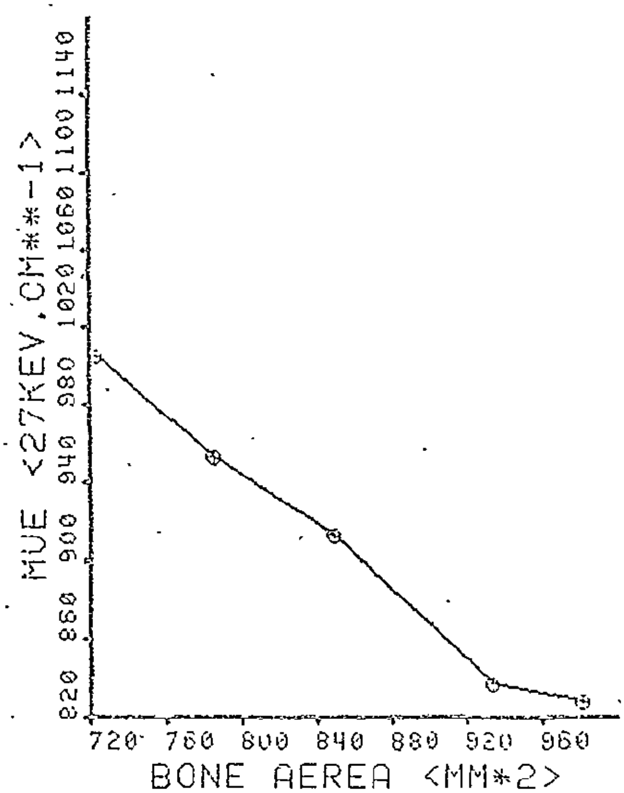


Fig.14: As in fig.13, for BF.

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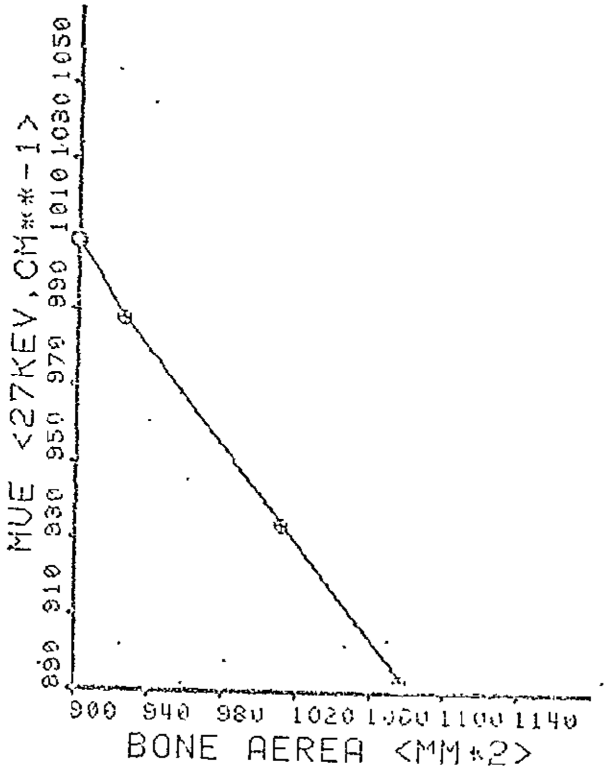

Fig.15: As in fig.13, for JD.

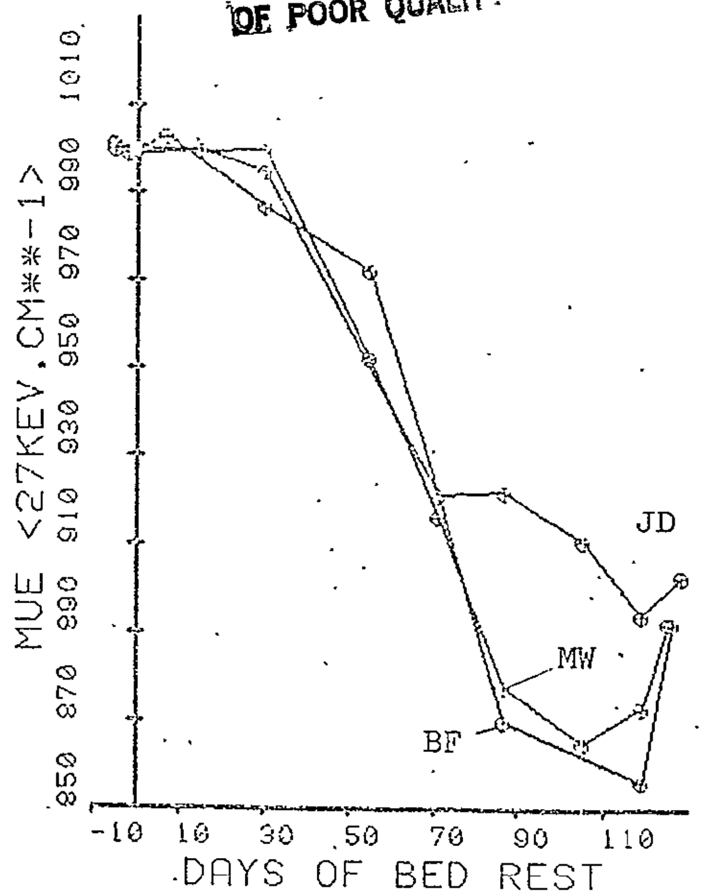

Fig.16: Mean bone attenuation coefficient relative to the base line mean bone attenuation coefficient as a function of time. Bedrest ends at day 119. Measuring site: Calcaneus.

- The evaluation of the CT-images was done in an operator independent way because results were needed fast, i.e. there was no time to check on each evaluation if the bone boundary was found correctly.

As a consequence of these shortcomings the study has to be regarded as a pilot study (Notably one yielding very interesting and promising qualitative results) and the results presented as preliminary results.

6.3 Results

Figure 9-16 show the results of the CT bedrest study. Figure 9-12 follow from measurements on the radius, Figure 13-16 from measurements on the calcaneus. The presented calibration curves show very clearly that the calibration data is indeed only marginally sufficient. However, the bone mineral changes versus time (Figure 12 and 16) show a high consistency and prove in a qualitative way that the precision of the method is very high, certainly below 1%. The following observations can be derived:

1. Both the radius and the calcaneus lose bone mineral during prolonged bedrest.
2. The calcaneus as a weight bearing bone loses almost double the amount of bone mineral lost by the radius.
3. The bone mineral loss starts only after about one month of bedrest.
4. The bone mineral in the radius starts increasing again before the bedrest period is finished.
5. The bone mineral content in the calcaneus seems to come to a stable value of about 85% in a asymptotical way (Figure 12).

6. The curve marked JD in Figure 12 is the one of the subject on medication - it appears to be different from the other two.

7. Conclusion

The CT-study in San Francisco has clearly shown that g-CT-techniques allow for a high precision high accuracy determination of the bone mineral content. The method can be proven to be superior to any other known method for the in vivo determination of the bone mineral content. The study was successful in several ways:

- A new repositioning method could be developed yielding a very high precision
- Bone mineral loss in the radius could be reliably shown for the first time
- For the first time the bone mineral content in the calcaneus was measured using g-CT-techniques. Measurements on the tibia (distal) were shown to be feasible.

There is no doubt in my mind that a continuation of this study would yield very interesting and quantitative reliable results.

EXPERIMENTS DEVELOPMENT

The development of inflight experiments was one of the tasks of the contract. Considerable activity was expended and several potential inflight investigative protocols were developed. Many of these evolved into formal responses to the shuttle program's announcement of opportunity for flight experimentation. Since these are too numerous to include in this report, three representatives have been chosen for display.

BONE GROWTH AND REPAIR

IN

WEIGHTLESSNESS

BONE GROWTH AND REPAIR IN WEIGHTLESSNESS

TABLE OF CONTENTS

ABSTRACT

A. Flight Experiment Title:

BONE GROWTH AND REPAIR IN WEIGHTLESSNESS

B. Purpose:

The purpose of this investigation is to better define the process whereby the mineral content of bones is decreased in null gravity space flight and to determine the rate and quality of bone repair in response to an experimentally induced lesion. During space flight, a negative calcium balance has been found in crewmembers and has been associated with variable slight decreases in the mineral content of the os calcis. Experience has shown that the process is progressive for as long as space flight is continued. More recent studies on laboratory rats flown for 18 to 22 days onboard the Cosmos biosatellites have revealed that osteoblastic activity is almost completely inhibited following the onset of weightlessness. On return, histologic changes were found in weight-bearing bones indicating a decrease in the rate of periosteal bone formation with no apparent change in resorption. The proposed study will focus on changes in the growth and repair in the laboratory rat's femur, in the animal's total body calcium, and gastrointestinal calcium absorption. Small lesions will be produced in the bone to determine total calcium. Tettracycline labels will be used to determine the rate of bone deposition. A tomograph will be used to determine the density of cross sections of cortical and trabecular layers of normal and healing bone. The data obtained from the flight group will be compared to a ground-based control. Two flight groups will include rapidly growing animals similar in size to those used in the Cosmos biosatellite studies and mature slower growing animals.

C. Applicable Life Sciences Speciality:

Musculoskeletal

1.0 Objectives

1.1 Hypothesis and Expected Results

It is hypothesized that when laboratory rats are exposed to weightlessness for 8-10 days one or more of the following events will occur.

a. There will be a decrease in the rate of both endosteal and periosteal bone formation.

b. There will commence a progressive rarefaction of the bones mineral and organic substance and a loss in total body calcium.

c. There will be an elevation in the level of serum phosphorus and calcium.

d. There will be an increase in the urinary excretion of calcium and phosphorus and a progressive inhibition of the gastrointestinal absorption of calcium.

e. The healing of induced fractures in space will proceed at a slower rate and will result in the production of new bone which is mechanically weaker than that produced by ground-based controls.

Previous experiments have demonstrated that, when male Wistar rats are exposed to the weightlessness of orbital space flight, periosteal bone formation is greatly diminished. Studies on man exposed to weightlessness for up to three months have demonstrated the rarefaction of bone, the loss of its mineral and organic substance from the body, and a progressive inhibition of calcium absorption. These changes were accompanied by increases in serum calcium and phosphorus and by a gradual diminution of parathyroid hormone excretion.

It is hypothesized that the changes observed in man will be seen also in the rat and that the retardation of osteoblastic activity will adversely affect the ability of bones to repair in weightlessness.

In this experiment particular care will be taken to ensure that animals sent into space and their terrestrial controls are given comparable quantities of all nutrients and especially of calories. It is conjectured that differences in nutrient intake may have confounded earlier space flight observations of rats.

1.2 Background

X-ray densitometric measurements of the heel before and after the Gemini space flights which lasted 4-14 days initially demonstrated that very rapid rates of mineral loss are associated with space flight (1). However, probable errors associated with Mack's original observations were later recognized and a lower estimate of mineral loss in space flight was computed (2).. In the two Soyuz-9 cosmonauts, bone density was measured preflight and postflight. It was noted that exposure to weightlessness for 18 days caused a decrease in the radiographic density of the heel to

levels characteristic of a 62 to 70-day confinement of a healthy man to a strict bed rest regime (3). Measurements made in a subhuman primate after eight days of weightlessness showed similar losses in a wide variety of anatomic sites (4).

During the 14-day flight of Gemini VII a metabolic balance study was performed on the two astronauts. In one man, significant increases in urinary calcium occurred during the second week of flight and calcium balance became less positive in flight in both subjects (5). A similar study performed in association with the 13-day lunar flight of Apollo 17 showed increases in both urinary and fecal phosphorus and increased fecal calcium in the three astronauts. The data from Apollo 17 suggested decreased absorption of alimentary calcium (6).

In the short Gemini and Apollo studies operational considerations prevented the acquisition of sufficiently precise data to enable meaningful kinetic studies to be made on the effects of space flight on urine and fecal calcium loss. Such an opportunity was afforded by the 3 long-term Skylab flights. During each of these missions a different complement of three crewmembers occupied the Skylab spacecraft and orbited the earth at approximately 430 kilometers for 28, 59, and 84 days (7, 8).

Within one day following insertion of the Skylab crewmembers into the weightlessness of orbital flight the quantity of calcium appearing in the urine began to increase (Figure 1). Within 10 days the positive calcium balances which prevailed preflight were abolished and the body as a whole began to lose calcium (Figure 2). The loss was slow at first, amounting to about 50 mg per day at 10 days, and then increased dramatically to almost 300 mg per day by the 84th day of flight. Examination of the data reveals that at the end of 84 days in flight, the average Skylab crewmember had lost approximately 25g of calcium from his overall pool of the element. From this it is evident that approximately 2.5% of the pool is depleted in this period of time (9).

Within thirty days following the onset of weightlessness the quantity of calcium appearing in the urine leveled out at approximately 100 percent above preflight levels. This level of excretion was maintained for the remainder of the flight. During the postflight period the quantity of calcium excreted in the urine fell very rapidly to levels lower than preflight. The calcium content of the stool exhibited a quite different pattern of excretion. It fell initially to levels below preflight and thereafter rose, in an apparently linear fashion, until the end of the flight after which it tended to return toward preflight levels.

In the Skylab flights an increase in bone resorption or a decrease in bone formation might have led to the observed increase in serum calcium and phosphorus concentrations (10). These elevations caused an increased urinary concentration either by increasing the filtered load or by suppressing parathyroid hormone secretion.

The mechanism for the fecal calcium increase is more obscure. Calcium absorption is controlled to a large extent by the hormonal metabolite of

vitamin D_3, 1,25-dihydroxy cholicalciferol. This metabolite was not measured but its 25 hydroxylated precursor was measured. This metabolite was slightly decreased postflight in the Skylab 4 crewmembers but unchanged in the other six Skylab members (10).

Surprisingly, the C terminal metabolite of parathyroid hormone initially showed slightly increased levels in flight, concurrent with the already noted increase in serum calcium (10). Later a reduction in parathyroid hormone might have resulted in the reduction in the gastrointestinal absorption of calcium. In the kidney, parathyroid hormone stimulates renal reabsorption of calcium and at the same time stimulates production of 1,25 dihydroxycholecalciferol from 25 hydroxycholecalciferol. The 1,25 dihydroxycholecalciferol, besides stimulating renal reabsorption, stimulates calcium absorption (11). Increased levels of cortisol also may have contributed to the malabsorption (10). The glucocorticoids have been postulated as having a primary causative role in the pathogenesis of postmenopausal and senile osteoporosis (12). At least in the human, the free cortisol changes do not seem great enough to cause a significant loss of bone substance since the values are considerably below levels found in Cushing's disease and the duration of effect was too short for the calcium balance change noted in Apollo and Gemini crews. The same is true of thyroid hormone changes. Aldosterone excretion increased two or three times; serum sodium decreased about 4 meg/l, and the plasma volume decreased about 10%. These changes would affect resorption of calcium by the kidney.

Although the data would suggest the development of progressive malabsorption of calcium, the possibility of increasingly large amounts of calcium being secreted into the gastrointestinal tract cannot be discounted.

Within approximately three months following the end of the 84-day flight, the mineral mass of the calcaneus had returned to preflight values (13). During reambulation, calcium balance tended to become more positive, although it did not return to baseline levels within the eighteen-day period of postflight observations. The evidence suggests and it is, moreover, tacitly assumed that after a period of time subjects return to positive calcium balance and that the skeletal structure returns to normal.

A more ominous possibility is suggested by the work of several investigators who have studied the reversibility of osteoporosis. Lindgren and Mattson, for instance, subjected rats to nine weeks of partial immobilization followed by 10 weeks of normal activity. No evidence was found of any reversal or repair of the induced osteoporosis (14). Schneider, et al, studying middle-aged men after six weeks of bed rest, demonstrated a tendency for the subjects to resume a condition of zero balance long before the calcium loss had been repleted (15). The suggestion is inescapable that long term bed rest and possibly space flight causes permanent and cumulative damage and that the nine-month or so flight duration limit that has been suggested might actually represent a nine-month lifetime exposure limit (7). It is, of course, well recognized that substantial destruction of trabecular architecture is irreversible (12). The question that is raised here is whether earlier damage does not have equally long lasting effects.

Classically, disuse osteopenia has been thought to be due to mechanical factors such as the absence of pressure transmitted to bone or to the absence of tensile and shearing forces applied to bone by muscle (16). A variety of data are available to support this conclusion. It has been demonstrated that compression of the head of the tibia by a special clamp results in increased bone deposition in the compressed area (12). Observations in mice and chicks subjected to continual centrifugation at 4 and 5 g also demonstrate stimulated bone growth (12). Kazarian and Von Gierke, studying immobilized Macaca Mulatta monkeys showed enhanced bone resorption at the sites of muscle insertion onto bone (17).

The fundamental mechanism by which calcium loss occurs is presumed to be primarily increased bone resorption rather than decreased bone formation. In view of this generally held belief, it is surprising that during a 27-day flight of rats aboard the Cosmos 605 satellite, investigators noted an increase in lacunar canalicular pore diameter over ground-based controls and a decreased rate of periosteal bone formation of approximately 40% less than controls. An arrest line was found at both the endosteum and periosteum of the flight animals suggesting that a complete cessation of bone growth occurred during flight (18). Microscopic examination of the femur, tibia and humerus of Wistar rats following a 19.5-day space flight aboard Cosmos 782 showed decreased metaphyseal bone which was actually combined with a decrease in spongy mass in the vicinity of the epiphyseal cartilagenous plate suggesting an inhibition of bone growth during flight (19). These results are viewed somewhat equivocally because of the observation that centrifugation of rats at 1-g on the 18-day flight of Cosmos 936 failed to correct the retardation of bone formation (20).

In these Cosmos flights the well known effects of changes in nutrient intake on bone growth cannot be completely ruled out since the flight rats gained less weight than their ground-based controls. It is recognized, for example, that changing from a 0.6% to 0.025% calcium diet can cause a significant decrease in bone mass (22). In addition, caloric restriction can have dramatic effects on the bone growth in young rats. For example, a 50% caloric restriction even with normal calcium intake can cause complete cessation of skeletal growth (22). This is not the case for rats which are beyond the rapid growth phase such as the 200 day old rats to be used as one element of this experiment.

The intermittent pressure on the os calcis during programmed exercise in Skylab might have affected the calcium loss. However, bed rest studies have shown generally that isotonic exercise cannot prevent calcium loss. In bed rest studies even 3 hours of quiet standing per day or a similar period of bicycle ergometery exercise failed to reverse a negative calcium balance (15, 23). Vogel, et al, who analyzed and performed the photon absorption densitometry of the os calcis, radius and ulna noted that calcium loss from these narrowly defined bone areas was similar to that found in bed rest studies although only three crewmembers showed a mineral loss great enough to be significant statistically (13). Since the negative calcium balance of the Skylab crewmembers tended to be greater than that recorded in bed-rested subjects, we can postulate that if the exercise had a sparing effect on the bones measured then the bulk of the calcium loss noted in the balance study came from other areas of the skeleton.

Certainly nothing approaching the dramatic changes found in the Russian flight animals occurred or was measured in the Skylab crewmembers. For example, the crewmember densitometry showed no change greater than 7% even after 84 days of flight (13). This compares with 10% (flight vs synchronous) or 20% (flight vs vivarium controls) found in the rat femur studies after only 22 days of flight (18). The most likely explanation and the one to be tested in this experiment is that the rat, when it is growing rapidly, is exquisitely sensitive to any change in calcium supply produced by flight conditions. The rapidly growing rat normally absorbs nearly all its daily food calcium. This suggests that calcium balance is marginal and that any change could produce a profound effect. This is not true later when growth slows to a low rate.

At the age of the U.S. crewmembers (5th decade) resorption of bone calcium is greater than accretion since the human skeleton tends to lose calcium gradually starting in the third decade (12). This contrasts sharply with the rapidly growing flight rats of the Russians.

The present study is designed to verify the possibility that decreased calcium absorption combined with a high daily calcium requirement causes the observed dramatic cessation of bone formation in the rat. It is proposed to employ mature animals in order to induce bone injury since bone healing will probably be the only process adversely affected by a space flight of only one week in duration.

1.3 Relevance to the Medical Problems of Space Flight

No study has been made of the effect of near zero-g on the early phases of fracture repair when accompanied by the negative calcium balance and the decreased osteoblastic activity of weightless flight.

The present study should help answer the following questions:

a. What causes the negative calcium balance: decreased accretion, increased bone loss, or a combination?

b. Is the decreased calcium absorption primary or is it secondary to not eating?

c. What is the location in the skeleton of the calcium loss?

1.4 Justification to Fly in Space

It is unknown why space flight causes negative calcium balance in the crewmembers. Prior to the flight era, prognosticators published reviews which stated that a negative calcium balance would occur. These were proven to be correct by the metabolic studies of Gemini 7, Apollo and Skylab. The accumulating data indicates that significant differences exist between the findings from space flight crewmembers and bed-rested subjects.

These include a failure of the elevated urine calcium to subside during space flight and the greater mineral loss from the os calcis in the bed-rested subjects.

The negative calcium balance associated with bed rest has been studied extensively and often recorded. Still, the mechanism producing the change is essentially unknown. This is even more true of space flight. Therefore, if one is to study the causes of the negative calcium balance of space flight, one must use flight crewmembers, flight passengers or laboratory animals.

NASA-S-78-10758

CHANGE IN URINE CALCIUM DURING THE FIRST FOURTEEN DAYS OF SKYLAB FLIGHT

MEAN ± SE

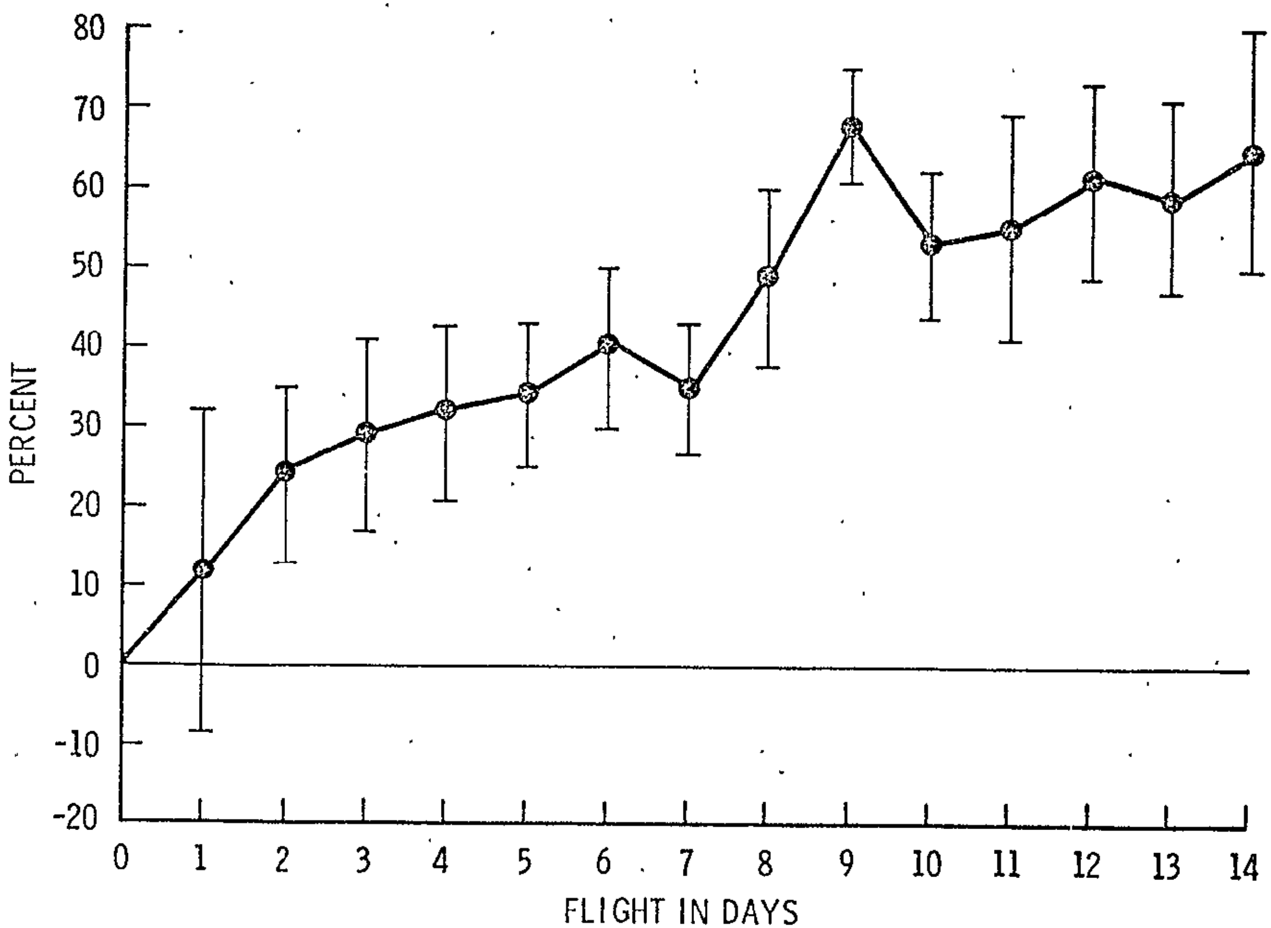

Figure 1

NASA-S-78-10774

CALCIUM BALANCE AS A FUNCTION OF SKYLAB FLIGHT DURATION

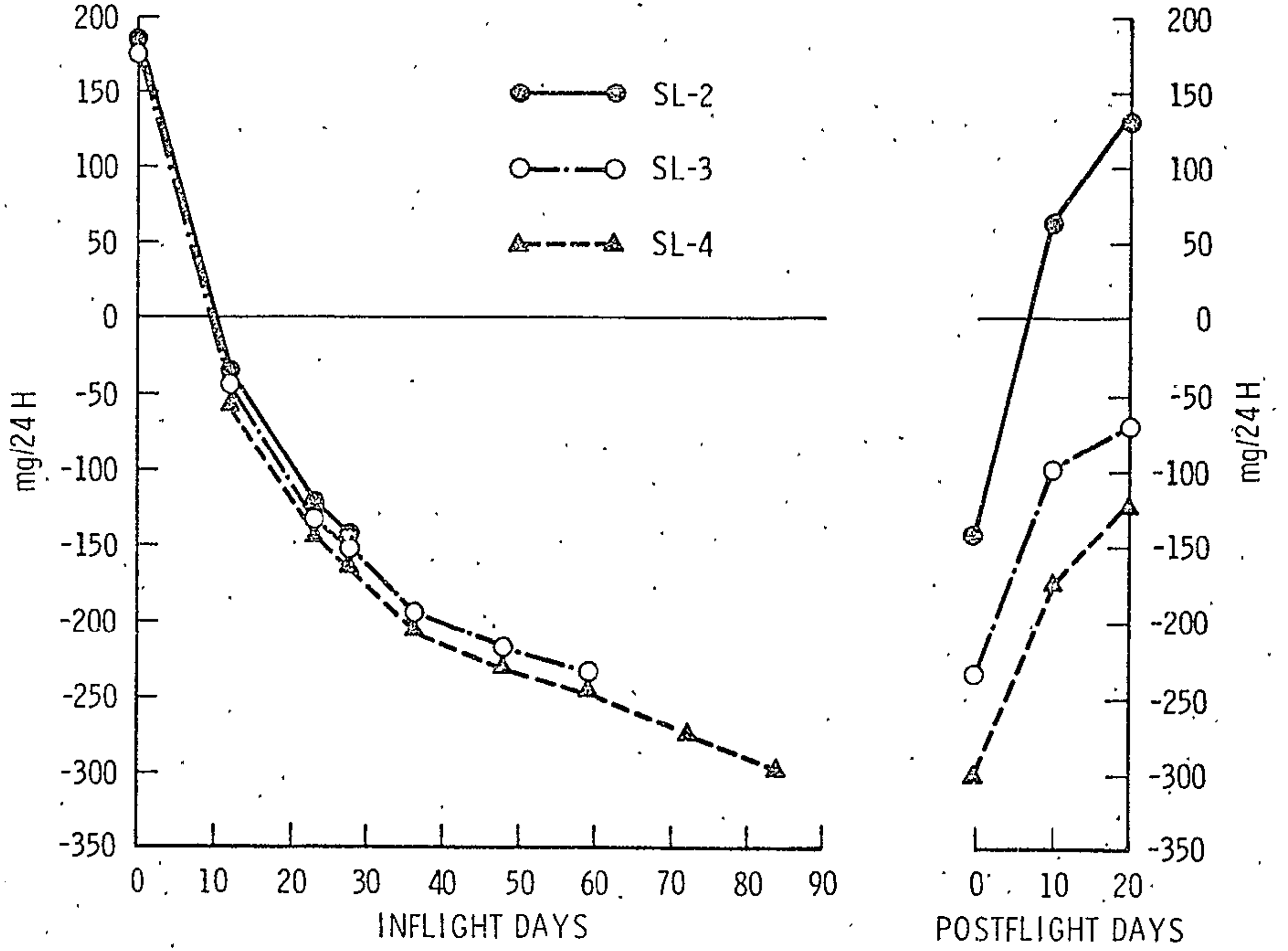

Figure 2

2.0 General Approach

The general approach to assessing bone growth and repair during weightlessness will be to drill a series of small holes in the femurs of rats before exposing them to 0-g. It is believed that the drilled holes will be similar to microfractures which develop and heal during normal activity on earth. The rate of healing and the quality of the new bone formed during weightlessness will be compared to that of ground based controls. The quality of bone formed will be assessed by radiographic, pathological and penitrometer techniques.

2.1 Experimental Design

Animals used in this experiment will be female SPF Sprague-Dawley rats which will be obtained from Ames Research Center.

F-30 - Animals arrive at NASA/JSC animal holding facilities

F-24 - Measurement of total body calcium content and tomograph scan, all animals

F-17 - Measurement of total body calcium content and tomograph scan, all animals

F-10 - Measurement of total body calcium content and tomograph scan start animals on chow with tetracycline-A, (continue until F-3)

F-8 - Transport animals to NASA/KSC

F-7 - Biopsy and drill holes in right femur, see surgical procedures 2.2.2

F-3 - Biopsy and drill holes in left femur, see surgical procedures 2.2.2 discontinue food with tetracycline-A, receive plain ground chow paste diet

F-0 - All animals receive diet with tetracycline-B, this will continue throughout the flight period.

F+4 - All animals receive ^{47}Ca I.P. and ^{45}Ca via gastric intubation

R+0 - x-ray and sacrifice all animals and return to NASA/JSC

R+2-4 Measure total body calcium content and tomograph scan of lesions

R+4-5 Autopsy animals

R+5-20 pathological sections Examined

R+28 1st conference on results

R+90 Final report of results

2.2 Experimental Procedure

Animals will be received at the designated animal holding facility at F-30 days. Following a brief adjustment period, weekly measurements of total calcium content will be made by means of whole body neutron activation. Weekly tomographic images of the area to be lesioned will be made with a densitometer. These measurements will allow us to document those changes normally occurring in growing rats. At day F-10 all animals will begin receiving tetracycline-A labeled ground chow diet. The animals will be transported to the animal holding facilities at NASA/KSC on day F-8. Surgery will be performed on all animals on days F-7 and F-3. (see section 2.2.2 Surgical Procedure). High speed drill bits (1.0 - 0.45 mm) will be used during this procedure. It has been found in our laboratory that the use of high speed drills minimizes tissue burning and injury as well as minimizing trauma to the animals. It is believed that the drilled holes, in this size range, will simulate microfractures which develop and heal during normal activity on earth. In addition, this type of injury will not immobilize the animal.

A core sample will be obtained in the same region via a specially designed biopsy drill. The diameter of the core sample will be similar to that of the drilled holes (external diameter 1.0 mm, internal diameter 0.8 mm). The core sample will be placed in the appropriate fixative for future examination. The core sample will be used as a control for post-experimental pathological studies. Photographs of the exposed lesioned area will be made prior to closure in each animal.

The animals will be sutured subcutaneously with gut suture to minimize the possibility of infection or opening of the wound.

Following surgery on F-3 through launch the animals will receive a diet of unlabeled ground chow in paste form.

After launch all animals, ground-based and flight, will receive a diet labeled with tetracyclin-B. This diet will continue for the duration of the flight. On day F+4 all animals will receive ^{47}Ca I.P. and ^{45}Ca via gastric intubation. Feces and urine filter will be collected and saved for the remainder of the flight for later analysis. During the flight period all necessary maintenance will be performed, but the animals will not be subjected to any procedures which may cause additional trauma or interfere with the experimental results. The mission specialist will keep a log book noting the general activity and appearance of the animals. Postflight the flight animals will be returned to the investigators, as soon as possible, (within 4 hours), for postflight examination and sacrifice. All animals will be sacrificed after the appropriate testing regimens are complete. This will be done in a humane manner in accordance with standard recognized procedures.

All animals will be x-rayed for gross evaluation of healing and tomographic images of the lesions will be made to help quantify bone formation. The animals will then be returned to Houston for whole body neutron activation to determine total body calcium content.

Animals will than be necropsied with careful examination of all tissue surrounding the lesioned area. Complete reports will be recorded of the gross examination, thereby becoming a permanent part of the animals record. The femurs will be removed routinely and fixed in an appropriate fixative for pathological and penitrometer examination. Flight animals will be compared to ground-based controls as well as to their own preflight core samples. A penitrometer will be used to measure the tensile strength of the newly formed bone in the area of the drilled holes in each animal.

All animals that die during the experiment will be necropsied as soon as possible following death. Each animal will be subjected to the same examinations as those being sacrificed.

2.1.1 Animal Care

Animals used in this study will be female, Sprague-Dawley, specific pathogen-free specimens supplied by Ames Research Center. Animals will be housed in the proposed animal holding facilities at NASA/JSC and NASA/KSC.

Caging utilized in the performance of this experiment will be suitable to maintain the animals in a healthy environment. Ground-based controls and preflight test animals will be housed in standard hanging galvanized cages or immediately following surgery, in opaque plastic cages with absorb-dri bedding. Inflight animals will be housed in standard Shuttle facilities. Not to be slighted are the caging and housekeeping regimens required to maintain organismic homeostasis. Within this framework, caging involves all factors, including food and water, which may influence the end result - bone growth and repair; therefore, the following caging characteristics are proposed. The cyclic nature of organismic behavior has been well established, as a result, the care and feeding of the animals will be accomplished at approximately the same time each day without undue clamor or disturbance of the animals. Other animal caretaking chores will be on an established schedule. All animals will be fed Purina Ground Laboratory Rat Chow, which will be available in a paste form, and deionized water.

Cage size may effect animal morbidity, mortality, and food and water consumption. The effort to maintain animal thriftiness in the face of severe environmental caging difficulties can result in the loss of interpretation of, a no-change in the test animal. Such effects would negate the potential validity of the proposed study.

In addition to the cages being comfortable, sanitary and safe, they must be secure. To minimize escape, observations will be conducted without opening the cage except during necessary periods such as feeding or cleaning. The lighting system will be the indirect type which results in relatively even distribution of lights over a 12-hour light/dark cycle.

The food for the control and preflight test animals will be kept in a sealed container to prevent contamination, and stored at -17 $\pm$ 4°C. Records of the receipt and storage of animal feed will be maintained in bound log books, signed and dated by the appropriate individuals, and initialed by the supervisory personnel. Food for the flight animals will be stored in an appropriate designated area aboard the space Shuttle. Animal identification will be by means of a standardized system of ear punches.

When necessary, the animals will be transported, as quickly as possible in filtered cages in a temperature-controlled clean vehicle without being subjected to physical or psychological stress. Each animal or experimental group will be accompanied by their complete medical/clinical record. Surgical gloves and masks will be worn by all persons coming in contact with the animals.

2.2.2 Surgical Procedure

1) anesthetize animal with Nembutal and shave
2) take control x-ray
3) perform surgery-drill 3 holes and take bone biopsy from distal portion of femur
4) make penitrometer measurements
5) take postsurgery x-ray
6) scan area with densitometer
7) return animals to cage

It is anticipated that this entire procedure will take about 75 to 90 minutes per animal. All animals will be subjected to this procedure within an 8 to 10 hour time span.

2.2.3 Bone Biopsy

Bone biopsies are usually performed using a bone trephine; however, this is much to large an instrument to use in rat femurs. For this reason, we propose the use of a hollow core drill bit, external diameter 1 mm, internal diameter 0.8 mm. The bone tissue will be removed from the bit and placed in a fixative for later pathological examination.

2.2.4 X-Ray Procedure

X-Rays will be made on Kodak X-OMATIC-G film. The setting will be 24x30 sonometers, 200 MA at 1 second, 38 KVP at a 40" distance. Film will be processed in a Kodak M-6 processor for 90 seconds.

X-Rays will provide a method of qualitatively examining the lesion as well as aiding in positioning the animal in the densitometer. X-rays will be shipped to the Jet Propulsion Laboratories for image enhancement and analysis.

2.2.5 Tetracycline Label

The tetracyline label method is very sensitive and can be used to judge the character of bone reconstruction during callus formation. The tetracycline label method is simple, readily available, and provides objective evidence of the character of reorganization of the osteogenic structures during the early stages of callus formation (24).

Tetracycline-A will be incorporated into the animals food on days F-10 through F-3. The animals will be fed a ground chow paste, without a label, F-3 through launch. During the flight period all animals will be fed food labeled with tetracycline B. The use of two different labels (A and B) will allow observation of the difference of osteoblastic formation rates preflight and in flight.

2.2.6 Activation Analysis

These measurements will be performed before and after space flight using the neutron activation facility at Baylor College of Medicine (25,26,27). The neutron activation laboratory which is supported by NASA funds consists of the irradiation room and an adjacent counting laboratory. Within the irradiation room are located the neutron shield, irradiator, and neutron source which is 1.5 mg of ^{252}Cf, an isotope which spontaneously fissions

giving off neutrons with a mean energy of 2.3 MeV. The exit port of the irradiator is 20 x 30 cm. By means of collimator inserts, a uniform thermal flux and acceptable dose is obtained. A 5-cm thick plexiglass container with rectangular walls and a removable cylinder will be used to hold the rat. The cylinder is rotated (6 rev/min) during irradiation by a motor mounted in the wall. A plexiglass block is placed above the cylinder during irradiation to increase back-scattered neutrons. During irradiation ^{48}Ca, which has a natural abundance of 0.18%, captures a thermal neutron to produce ^{49}Ca which has a half-life of 8.7 minutes. ^{49}Ca emits a 3.1- MeV gamma ray which is used for quantitation.

The counting facility consists of two opposing 29-cm diameter by 10-cm thick NaI (Tl) detectors. ^{49}Ca activity is determined by counting the rat in the plexiglass cylinder during irradiation. The detector separation is approximately 10 cm. The pulse height spectra from the two detectors are recorded with a 1024 channel analyzer to a counting accuracy of $\pm$ 1%. ^{47}Ca gamma rays do not interfer with the counting of energetic ^{49}Ca gamma rays.

Multiple measurements of the same rat over a short interval have shown that the reproducibility is approximately $\pm$ 1.6%. The accuracy of this method for determining total body calcium of the rat has been verified by atomic absorption spectrophotometry after sacrificing and ashing the animal. The neutron activation analysis gives a 2.1% smaller value for total body calcium than does the atomic absorption method. The neutron and gamma radiation exposure per measurement is about 5 rads, giving a cumulative dose of 20 rads per animal. This amount of exposure does not produce detectable changes in growth and bone formation based on our observations and that of others (28, 29).

2.2.7 Computerized Axial Tomography (CAT)

In the CAT procedure developed by Anliker, (30), the width of the leg is linearly scanned during 128 parallel and equally timed intervals. The density value of each interval is recorded by a computer. The gamma beam is then rotated 1.885° and the linear scanning is repeated. This process is carried out 96 times until a semi-circle has been made about the sample. All of the internal values are then processed by the computer to reconstruct a cross-sectional image of the sample. The computer uses the convolution method to determine the geometric distribution of the local absorption coefficients (29) which are recorded as a matrix of 128 x 128 elements, or pixels. The absorbtion coefficients are assigned different shades of gray, based upon their magnitude. The reconstruction is then displayed as the color-coded representation of the 128 pixels, allowing the visualization of the density distribution. Soft tissue is removed from the determinations of bone density by removing the appropriate density. Trabecular bone is isolated in the same manner by removing the cortical bone density. The advantage of the computed tomography over the x-ray and gamma-ray densitometric techniques is that, by mathematical reconstruction, it is capable of distinguishing small differences in gamma-ray densities which are too subtle to be detected by the other two methods.

The reproduciblity of this procedure is $\pm$1% for the trabecular bone measurements, $\pm$2% for the cortical bone and total mineral content (31). Computed tomography is a qualitative determination of mineral content and mineral

composition based upon a density distribution. Consequently, no quantitative analysis in terms of mineral loss in hydroxyapatite units can be given, but a reliable value of mineral density changes can be determined (31,32,34). Trabecular bone density can be quantitated to an accuracy of ±2% (35). The machine is easy to use, requires little time, and is the most sensitive instrument to date for the in vivo quantitative measurement of trabecular bone changes.

CAT scans will be made during the preflight stabilization and growth phase, after surgery, and postflight. They will not be performed in flight. These scans will be accomplished using equipment currently located in the Bone and Muscle Laboratory of the Johnson Space Center.

During the first preflight measurements a site in the trabecular region of the femur will be measured. The postsurgery and postflight measurements will involve scanning one of the lesions. These measurements will take approximately 40 minutes per scan for each animal.

2.2.8 Pathology Methods

The femurs will be radiographed in a high resolution unit, measured, weighed, fixed in cold 4% neutral buffered formaldehyde for 24 to 28 hours, dehydrated, and embedded in methyl methacrylate (35). The specimen will be subdivided by a low-speed diamond-wafering saw into identifiable cross-sections representing the different lesions and undisturbed bone. The latter will be the same distance from the proximal end of the femur in each of the rats. The blocks will be radiographed to locate, orient, and measure the cross-sectional diameter of the lesions. Each block will be cut with a low-speed saw (36) and a rotary microtome with glass knives (37) to produce 50-micron and 10-micron cross sections, respectively. Autoradiographic (35) and then microradiographic (36) observations will be made on identical sections of both thicknesses to identify gross changes in the thicker sections and changes associated with individual cells in the thinner. Histologic observation and documentation will be done on the unstained and subsequently stained thinner sections with a epifluorescent photomicroscope. Staining will be a modified von-Kossa-acid fuchsin to distinguish calcified bone, calcification front, and osteoid. Observations will include location of radioactive calcium (35); density of calcification (38); quantitative bone formation, resorption, calcification front, osteocytic osteolysis and fracture healing (35-39); and quantitative tetracycline labeling using the different emmision colors of the two tetracyclines to distinguish preflight and flight label (39). Serial autoradiographic, microradiographic, and histologic observations on identical sections will facilitate quantitative correlations.

2.2.9 Calcium Absorption

In order to determine if calcium is malabsorbed in space, a precalibrated mixture of 20 uCi of ^{45}Ca and 2 mg of $CaCl_2$ in a 1-ml solution will be given to each rat via a stomach tube on the fourth day of flight. The tube will be flushed with 3 ml of isotonic saline. Two mg of Ca is about 1/10 the amount of Ca normally eaten and absorbed per day by the young rat on a high calcium diet and therefore high absorption is expected. Older rats (6 months) ingest about 30 mg of calcium per day but only retain about 5 mg. (40) The regular rat food will be withheld for approximately 8 hours following ingestion of the ^{45}Ca. At the time the ^{45}Ca is given, 10 uCi of high specific activity ^{47}Ca dissolve in isotonic saline will be injected into the peritoneal cavity. Syringes will be labeled and saved for subsequent counting to correct for any residual activity in the syringe. After the return and sacrifice of these rats, the incisor teeth will be ashed by heating in a muffle furnace at 500°C for 12 hours and the ashes than dissolved in dilute HCl. The amount of the two isotopes will be measured by standard beta and gamma counting techniques and the percent uptake calculated after suitable corrections are made for radioactive decay and residual syringe activity. The ratio of the percentage uptake of the two isotopes is equal to the fraction of the ^{45}Ca, and therefore the calcium, absorbed by the gut. The absorbed dose to the rat from this procedure is estimated to be less than 6 rads. The dose rate at the surface of the rat cage is estimated to be 0.6 mr/hr and at 1 meter 0.2 mr per day. A conservative estimate of the radiation exposure to crewmembers from these radionuclides, including during their administration, is less than 10 mrad.

2.3 Implementation Requirements

2.3.1 Facilities

Ground-based measurements will be made at the NASA/JSC Buildings 8 and 37 and at the Technology Incorporated Laboratory, Clear Lake City. Animals will be housed in the proposed animal holding facilities at NASA/JSC. For the immediate preflight and postflight surgery the use of a room at NASA/KSC will be required as well as housing facilities for the KSC ground-based controls during flight.

2.3.2 Equipment

The following items of equipment and facilities will be required for the ground-based studies:

a. Animal housing

b. Bone drilling equipment

c. Densitometer

d. Normal clinical and laboratory equipment

e. Penitrometer

f. Bone biopsy punch (approximately 1 mm in external diameter, 0.8 mm internal diameter)

g. Buehler Isomet saw

Except for items e, f, g, this equipment already exists at NASA/JSC and Technology Incorporated. The Buehler Isomet saw will be purchased, and the penitrometer and bone biopsy punch will be developed as part of the preflight testing program.

The following equipment and supplies will be required for the orbital part of the study:

a. Animal housing
b. Tetracycline-treated food and deionized water
c. Gastric intubation equipment
d. Syringes and needles
e. ^{45}Ca and ^{47}Ca

The ground-based experiments will require supplies appropriate to the different procedures in use.

2.4 Operational Requirements

The performance of the experiment imposes no constraints on the orbital flight.

2.5 Payload Specialist

The payload specialist will be responsible for the daily maintenance of the animals. This will include supplying food, water, and clean housing facilities. On the 4th day on the flight the payload specialist will be required to inject the animals I.P. with ^{47}Ca and intubate them with ^{45}Ca. For the remainder of the flight the urine and feces filters from the animal cages will be saved for later evaluation by the investigators. It is also requested that the payload specialist keep a daily log of his/her observations of the animals. The log will include the time of day that general maintenance is performed as well as notes concerning the general health and appearance of the animals. It is anticipated that general

maintenance and record keeping will take approximately 15-20 minutes daily. A 1-hour time interval should be allocated on the day of gastric intubation.

2.6 Critical Constraints

In order to maintain the animals the environmental temperature must be maintained at 22.5 ± 4.5°C and their light cycle should be 12 hours light/dark. The light cycle will be synchronized with that of the ground-based controls. Relative humidity will be maintained at 40 to 60% in the animal housing.

2.7 Problem Areas

No problem areas are anticipated in conducting this experiment.

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BODY COMPOSITION STUDIES

INVESTIGATION AND TECHNICAL PLAN

Abstract

Purpose: Studies performed on Skylab showed significant changes to occur in all four (4) of the major body compartments - cell solids, bone mineral, fat and water. Changes in cell solids resulted principally from an exercise-related change in skeletal muscle mass. The present experiment is aimed at establishing the optimum type and quantity of inflight exercise, and to test they hypothesis that preflight physical conditioning is disadvantageous. Changes in bone mineral are not covered by the present study. Changes in body fat are related to caloric intake, and it is hoped to establish the normal inflight caloric requirements. Changes in water are believed to be due to the redistribution of body fluids in the absence of gravity, and the present experiment seeks to establish the magnitude and time course of this effect.

Specialities: Muscoloskeletal

Exercise physiology

Fluid and electrolyte control

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1.0 OBJECTIVES

1.1 Introduction

Previous studies on the effects of spaceflight on human body composition have indicated that changes occur in all 4 of the major compartments of the body - water, cell solids, bone mineral and fat (Whittle 1978a). The studies performed on Skylab indicated that the changes in body water (Leach and Rambaut 1977) and bone mineral (Vogel and Whittle 1974, Whedon et al 1977) are inevitable consequences of the exposure to weightlessness, the former apparently being self-limiting, and the latter progressive. The changes in cell solids are thought to have resulted partly from a reduction in red cell mass (Johnson et al 1974), but principally from an atrophy of skeletal muscle, due to relative disuse in the absence of gravity. The changes in skeletal muscle mass were related to the exercise taken inflight (Whittle 1978b). Changes in body fat were also observed, and these were significantly correlated with the inflight caloric consumption, enabling an estimate to be made of the caloric requirements of spaceflight. Copies of the papers (Whittle 1978a) and (Whittle 1978b) are included in the appendix to this proposal. A much more detailed account of this study is contained in a Ph.D. thesis (Whittle 1978c).

Despite the considerable progress made as a result of the Skylab experiments, further information is needed on the changes occuring in each of the 4 body compartments, as follows:

1) Cell Solids The loss of cell solids from red blood cells has been adequately covered by other experiments (Johnson et al 1974).

The muscle changes associated with spaceflight, however, need considerable further study if optimal exercise regimes are to be adopted for future spaceflights. It has long been thought that a high degree of physical fitness is advantageous for spaceflight, and most of the astronauts who have flown to date have undergone physical training programs prior to flight. However, this assumption has recently been seriously challenged (Klein et al 1977), with the suggestion that preflight physical conditioning increases both the extent of the inflight muscle atrophy and the degree of postflight orthostatic intolerance. It has been shown that a large amount of inflight exercise is needed to prevent muscle atrophy (Whittle 1978b), but it appears very likely that reducing the <u>preflight</u> exercise would reduce the requirement for <u>inflight</u> exercise. Inflight exercise is very time-consuming, and if the need for it could be reduced or eliminated, more time would be available for productive work in orbit. There are thus serious economic advantages to be gained from optimizing both the preflight and inflight exercise levels.

2) <u>Bone Mineral</u> The progressive loss of bone mineral is probably the most serious problem for very long manned spaceflights (Whedon et al 1977). However, the investigation of this problem is outside the scope of the present study.

3) <u>Fat</u> Caloric requirements on Skylab were found to be much higher than anticipated preflight (Whittle 1978b), and all but one of the astronauts lost body fat over the course of the flight. There has

even been a suggestion (Rambaut et al 1977) that caloric requirements many increase with the passage of time in zero gravity. It is essential, for the planning of future flights, to confirm the predictions of the level of caloric intake at which no change in body fat would occur, and thus to establish a baseline for future studies on the caloric requirements for very long flights.

4) Water It has been postulated (Leach et al 1970) that on exposure to zero gravity the venous tone in the legs causes the movement of blood into the central venous pool, resulting in an increased central venous pressure. This results in a negative fluid balance, previously thought to be mediated by the Henry-Gauer reflex, but since shown to be due to the supression of thirst (Leach and Rambaut 1977). There is, however, no direct evidence for this theory, and in particular little is known of either the extent or the time course of the movement of blood into the central pool.

1.2 Hypotheses and Expected Results

The proposed experiment should provide information on 3 different body components:

1) Muscle It is expected that the study will confirm the Skylab findings that a relatively high level of exercise is needed to prevent inflight muscle atrophy. However, it is also anticipated that reducing the exercise taken preflight will reduce the need for inflight exercise, without any adverse effects. Exercise devices simular to the Skylab treadmill (Thorton & Rummel 1977) will probably prove to be much more efficient than the bicycle ergometer, in preventing muscle atrophy, as well as being more economical

in the use of the astronaut's time. It is also thought possible that taking little or no exercise inflight could reduce the degree of postflight postual hypotension, although at the cost of producing a postflight weakness of the legs.

2) Fat It is expected that the inflight caloric requirement will prove to be in the range 47-51 kilocalories/day/kilogram lean body mass (LBM) for the majority of subjects (Whittle 1978b). It is not expected that the level of inflight exercise will greatly modify this estimate. Anonexia early in the flight will cause the majority of subjects to lose some body fat at the beginning of the mission, but if eating 'ad lib' is permitted, this loss will probably be made up before the flight ends. The relationship between the preflight basal metabolic rate and the inflight caloric requirement will be explored, but the results of such a study cannot be predicted.

3) Extracellular fluid It is expected that the shift of extracellular fluid from the lower limbs into the chest and abdomen will be confirmed, and that the magnitude of the fluid displacement will be about one liter. The measurements of pulmonary volumes early in the flight are expected to show a reduction in residual volume and expiratory reserve volume, due to the presence of additional blood in the lungs. It is anticipated that a return towards normal would occur during the first 48 hours inflight, but whether complete recovery will occur is unknown. Postflight the opposite situation is to be expected, with a reduced total body water, being most noticeable in the chest and abdomen. The time course of the recovery from this situation is expected to be 2-3 days.

1.3 Background

Whittle (1978b, 1978c) provided evidence for the postflight loss of muscle and showed there was a very high correlation between the inflight exercise on the bicycle ergometer, and the postflight change in volume of the thighs and calves (after correction for the change in volume due to fluid losses). The results of this experiment suggested that exercise levels of 81 watt-min/day/kg LBM were necessary to prevent atrophy of the thigh muscles, and 100 watt-min/day/kg LBM were needed to protect the calf muscles. These are very high exercise levels, being 30 - 60 minutes per day of hard cycling. Only 2 subjects on Skylab exceeded 81 watt min/day/kg LBM, and none exceeded 100. There would be a clear advantage to the program if it could be shown that such exercise levels are unnecessary.

Further confirmation of the changes in skeletal muscle was provided by Johnson et al (1977) who observed a progressive reduction in calf circumference over the course of the SL-4 flight, and by Thornton and Rummel (1977), who observed a marked reduction in leg strength postflight. The measurements of total body potassium (Leach and Rambuat 1977), and the results of the mineral balance experiment for nitrogen and potassium (Whedon et al 1977), all indicated a loss of cellular tissue from the body, although the magnitude of the loss, calulated from these experiments, appeared to be too great (Whittle 1978c).

Changes in the body fat of the Skylab astronauts were estimated in two ways - by attempting to determine the changes occuring in all the body compartments (Whittle 1978a), and by relating the caloric intake of the subjects to their changes in total body volume (Whittle 1978b). There was, unfortunately, only

a weak correlation between the two estimates (r = 0.69, significant at the 5% level), although they agreed that at least 7 subjects lost fat while in orbit, and that at least one gained it. The former technique estimated the mean change in fat to be -1.2 kg, and the latter -0.6 kg. Methods based on the measurement of total body volume, by whatever method, are likely to have a standard deviation of over 1 kg, and a different approach to the measurement of body fat will be required, to measure accurately the relatively small changes which may be anticipated on Shuttle/Spacelab flights. An examination of the energy balance of the Skylab astronauts (Rambaut et al 1977) showed the metabolic energy expenditure during flight to be higher than expected, and apparently increasing with the passage of time.

The studies of fluid shifts occuring as a result of spaceflight were reviewed by Pestov and Gerathewohl (1975). The removal of the normal hydrostatic gradient from head to foot results in a redistribution of blood on the venous side of the circulatory system, with an increase in central venous volume and pressure. This was thought to inhibit the production of antidiuretic hormone, by means of the Henry-Gauer reflex, and to cause a negative fluid balance for 1-2 days. The total body water then stabilized at about 1.4 kg less than normal, until the astronaut returned to earth, when the fluid volume was restored. Evidence for the theory came principally from the postflight reduction in weight and total body water, and from the inflight observation of increased pressure in the veins of the head and neck. Leach and Rambaut (1977) confirmed the loss of fluid from the body during the first few days inflight, although they were unable to

measure it with any accuracy. However, they found it was due to a reduction in intake, presumably through a supression of thirst, rather than through the Henry-Gauer reflex. The loss of fluid was estimated, principally from body mass data, to be 1-2 - 1.4 kg (Whittle 1978c), and the duration of the negative fluid balance was estimated to be 1-2 days. Thorton and Ord (1977) have suggested that at least part of the net loss of fluid from the body may have been due to anorexia, due to 'space sickness', rather than to the redistribution of the blood volume.

1.4 Relevance of Expected Results

Further examination of the relationships between diet and fat change, and between exercise and muscle change, may be expected to produce results of considerable importance to the manned spaceflight program. Before any very long term space missions can be undertaken, it will be essential to know the astronauts' metabolic requirements, so that spacecraft can be optimally provisioned with both food and oxygen. A knowledge of the type and quantity of exercise required by astronauts will enable their health to be preserved, without the expenditure of a great deal of time on unnecessary exercise.

The provision of further information on the fluid shifts occuring in spaceflight will help to further our understanding of the physiology of man in zero gravity. It is also possible that the negative fluid balance occuring early inflight is due to a hitherto unknown reflex mechanism, the elucidation of which would make a significant contribution to physiological research.

1.5 Justification for Conduct in Space

The changes in leg volume due to alterations in muscle mass are relatively small, and difficult to detect postflight, against the background of changes in body fluid. Accurate measurements of the changes in muscle mass could be obtained by making daily biostereometric measurements inflight, so that the cumulative changes in leg volume could be studied, at a time when the body fluid is stable. Similar considerations apply to the measurement of small changes in body fat, by examination of volume changes in the abdomen, buttocks, and whole body. Biostereometric studies early in the flight, in conjunction with measurements of fluid compartments, would give a valuable insight into the magnitude and time course of the redistribution of fluid occuring at this time, and by using the biostereometric equipment as a plethysmograph, the effect on lung volumes could also be measured. Such experiments could only be conducted inflight.

2.0 APPROACH

2.1 Experimental Design and Subjects

The experiment will be described in four parts - preflight, inflight, postflight, and background studies.

2.1.1 Preflight

It is anticipated that preflight and postflight examinations of test subjects will be conducted on two flights, whereas inflight investigations will be performed, at least initially, on only one flight.

The object of the preflight examination is to determine, as completely as possible, the body composition of the subject. To this end, the following measurements are proposed:

a) Body mass, by accurate clinical scales.

b) Total body water, by $^{3}H_2O$ dilution.

c) Total body potassium, by ^{40}K counting.

d) Body volume, by underwater weighing.

e) Biostereometric analysis, by stereophotogrammetry.

f) Basal metabolic rate, by oxygen consumption.

g) Bone mineral measurement (Tomography).

Measurements (a) to (d), and (g), provide the most accurate description of gross body composition available by present-day methods (Whittle, 1978c). All of these methods are in regular use, in either clinical or research laboratories. Total body bone mineral could be measured by in vivo neutron

activation analysis, although for the present purposes it would probably be sufficient to estimate it from total body potassium, or from anthropometric measurements (Allen et al 1959). It is anticipated that some of these measurements will be obtained by other investigators. However, it is important that measurements (a) to (e) are all performed within a few hours. Measurements (f) and (g) are unlikely to change significantly during the preflight period, and may be performed at any time.

Both underwater weighing and biostereometric analysis are included because, at present, underwater weighing is more accurate than biostereometric analysis for the <u>absolute</u> measurement of body fat, whereas biostereometric analysis, by its ability to examine different regions of the body, is better able to detect small <u>changes</u> in body fat, fluid and muscle (Whittle, 1978c).

Subjects for the experiment will be the payload specialists, and, if approved, also the pilots and mission specialists. Prior to the flight a detailed dietary and exercise history will be obtained, to determine the normal levels of caloric intake and exercise for each subject. The number and timing of the preflight measurements is to be decided.

2.1.2 <u>Inflight</u>

Two different inflight protocols are required - one for the flight in which body composition studies are to be performed only on the ground ('ground-based study'), and one for the flight on which inflight biostereometric analysis is to be performed ('inflight study').

1. <u>Protocol for ground-based study.</u>

   a) The subjects will be encouraged to adopt widely varying inflight exercise regimes.

   b) If approved clinically, at least one subject should perform no inflight exercise.

   c) Detailed recording inflight caloric intake is required.

   d) Detailed recording of inflight exercise is required.

   e) Daily body mass measurements are highly desirable.

2. <u>Protocol for inflight study.</u>

   Items (a) to (d) as above.

   e) Daily body mass measurement is required.

   f) Daily biostereometric analysis is required.

   g) Biostereometric analysis will be performed as soon as possible following launch, and several times (to be decided) during the first 48 hours of the flight, to study the redistribution of body fluids during this period. Ideally, this study should be combined with measurements of body fluid compartments.

   h) During the first 48 hours of the flight, details are required of the timing, and the approximate mass or volume, of all food and drink taken, and of all urine and feces voided. These data are required to interpret the regional volume changes determined by biostereometric analysis.

   i) The biostereometric apparatus will be used several times inflight as a whole-body plethysmograph, to determine the residual volume of air in the lungs, which is likely to be reduced by the increase in the volume of the central venous pool.

j) The effect of exercise on the distribution of body fluid will be examined, for different types of exercise, by performing biostereometric analysis before and after the exercise.

k) Subjects for the experiment would be the payload specialists on a given flight, and other Shuttle crewmembers, if approved.

2.1.3 <u>Postflight</u>

a) Items (a) to (f) of the preflight studies (section 2.1.1) will be repeated within 24 hours of the end of the flight.

b) Biostereometric analysis and body mass determination will be performed (i) immediately following the flight; (ii) daily, following sleep, for 5 days; (iii) thereafter at weekly intervals, for 4 weeks.

c) As far as possible, caloric intake and exercise should be monitored during the postflight period.

d) The results of postflight measurements of orthostatic intolerance are required.

2.1.4 <u>Background Studies</u>

In order to interpret fully the results of the biostereometric analysis, it is essential to perform two types of background study (Whittle, 1978c):

a) To establish the changes in regional volume distribution brought about by changes in body fat, muscle and fluid. This study would require subjects to alter their dietary or exercise regimes for a period of time, and to examine the resulting changes in regional body volume. The experimental subjects would be volunteers (probably members of the laboratory staff).

b) To establish the relationship between the results of body volume measurements by biostereometric analysis and by underwater weighing, and to eliminate any discrepancies between the two methods, such as those described by Luft (1975).

In addition to the above studies, and in conjunction with them, it would be of enormous benefit to the scientific study of human body composition if the full range of body composition studies (items (a) to (g) in section 2.1.1) could be performed on the subjects during the dietary and exercise experiments.

The biostereometric technique is expensive in terms of the manpower required for stereoplotting. An even more useful research program would be possible if the financial barriers to repeated measurement could be removed, by the development of an automatic system.

2.2 Procedures

With the exception of the inflight biostereometric study, all of the measurements would be performed in the investigator's laboratory, using established procedures and data storage techniques.

The inflight biostereometric study would generally follow the procedures established for the SIM/II ground-based Spacelab simulation, in which one crewman set up the apparatus, all the crewmen were photographed, and the apparatus was then dismantled and stored. It is anticipated that the use of roll-films instead of glass plates would further simplify a procedure that the crewmen found particularly trouble-free. The apparatus and

techniques are generally similar to those used preflight and postflight on the Skylab study, and described in Appendix 2.

2.3 Implementation Requirements

2.3.1 Facilities

Ground-based measurements would be made in the Bone and Muscle Laboratory it is hoped to establish in NASA/JSC Building 37, and at the Technology Incorporated Off-Site Laboratory, Clear Lake City. NASA computing facilities in JSC Building 12 (Univac 1108/1110) would be used for biostereometric data reduction.

For the immediate preflight and postflight biostereometric measurements, the use of a room at NASA/KSC will be required, to make the measurements as near as possible to the time of launch and landing. No other facilities will be required at JSC or KSC.

2.3.2 Equipment

The following items of equipment will be required for the ground-based studies:

a) Biostereometric facility
b) Underwater weighing facility
c) Whole body radioactive counter
d) Respiratory measurement equipment
e) Normal clinical and laboratory apparatus

Except for item (b), these already exist at NASA/JSC and Technology Incorporated. The underwater weighing facility will need to be built, and technicians trained it its use.

Regarding item (a), the biostereometric facility, an early decision will be needed as to whether to use existing methodology, which was shown on Skylab and SIM/II to be extremely reliable and accurate, but which is very expensive in terms of cost-per-measurement, or whether to develop a new automatic system. The latter will probably be slightly less accurate then the present system, at least initially, but would benefit the study by enabling a much greater number of analyses to be made.

The following equipment will be required for the orbital part of the study:

a) Cameras (4)

b) Strobe-projectors (2)

c) Power packs (2)

d) Calibration stands (2)

This equipment was developed by the Biostereometrics Laboratory, Technology Incorporated, Life Sciences Division under a NASA contract, for use on ASTP, SIM/II and crew selection physical parameter archiving, although some modifications would be needed prior to it use in orbital flight. However, if an automatic biostereometric technique is developed, it would be advantageous to use it for orbital as well as ground-based studies.

2.3.3 Supplies and Softwear

The only supplies required for the orbital part of the experiment will be replacement films or glass plates for the cameras.

The ground-based experiments will require supplies as appropriate to the different procedures in use. Computer analysis will be performed off-line, and softwear will be developed, as required, by the investigator.

2.4 Operational Requirements

The performance of this experiment imposes no constraints on the orbital flight, except that to gain maximum value from the experiment, the flight should be as long as possible.

2.5 Payload Specialist Requirements

For the ground-based experiments, the subjects will be required to spend 2-3 hours in the investigators' laboratory once before and once after the flight. In addition several further biostereometric analyses will be performed both before and after the flight. This takes approximately 5 minutes per subject, and can be done at any convenient location. The subjects will also need to obtain daily body mass measurements, and to report daily caloric intake and exercise, before, during and after the flight.

For the orbital experiments, one payload specialist will need 2-3 hours training in the equipment and procedures. The biostereometric analysis will take one payload specialist about 10 minutes for setting up and dismantling, and will require each subject for 2-3 minutes while the measurement is made. Time will also be required for changing films or plates, but this will depend on the details of the equipment adopted.

2.6 Critical Constraints

The biostereometric apparatus is precision optical equipment, and will need suitable packing to protect it during launch and recovery. The films should be protected from extremes of temperature, and from excessive radiation.

2.7 Problem Areas

No major problems are to be expected in the conduct of this experiment.

Minor problems may be anticipated as follows:

a) Inaccuracies in reporting caloric intake and exercise. The former could be overcome if each food or drink item was opened by a tear-off strip, which could be 'filed' by the crewman for later reporting.

b) Agreement of subjects to perform very high or very low levels of inflight exercise.

c) Difficultly in obtaining biostereometric studies close enough to launch and landing, due to scheduling constraints.

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APPENDIX 1 - PROJECT PERSONNEL

Co-Principal Investigator: Dr. Michael Whittle

Dr. Whittle was educated at Haberdashers' School, London, followed by the Universities of London and Surrey. He obtained a Bachelor's degree in Physiology, a Master's in Biomedical Engineering, and Doctorates in Medicine (M.D.) and Human Biology (Ph.D.).

Following his internship Dr. Whittle performed research on gastrointestinal physiology and medical education, before returning to college to study for a Master's degree. He then joined the Royal Air Force as a full-time research M.D., working at RAF Institute of Aviation Medicine, Farnborough, on the problems of high altitude flight, and aircrew protection. He was invited as a RAF fellow to the USA to spend 2-1/2 years at NASA/JSC, and acted as Principal Coordinating Scientist for the Skylab musculoskeletal studies. Following his return to Britain, he studied for a Ph.D. degree, based on the Skylab body composition studies.

Dr. Whittle has published a large number of papers, and has given presentations at many meetings, mostly on the subject of the changes in body composition associated with spaceflight. His Ph.D. thesis is a comprehensive study of this subject. As a result of his work on the Skylab experiments, he was awarded the NASA/JSC Certificate of Commendation, and the Royal Air Force Richard Fox-Linton Memorial Prize. One of his papers received the

Aerospace Medical Association Award (1977) for the Best Paper in Space Medicine, and he was elected Associate Fellow of the Association in the same year.

Co-Principal Investigator: Dr. Edwin B. Smith, Jr.

Dr. Smith as a Project Leader for Technology Incorporated was responsible for establishing the experimental protocol, writing any procedure manuals, and initiating training and coordination of laboratory personnel in support of Apollo 16 and 17, Skylab, SMEAT, ASTP, SMS-II, and SMD-III. Documentation trees in support of the M070 "Nutrition and Musculoskeletal Function" were prepared and utilized throughout the Skylab program. He directed the laboratory involved in nutrient intake and excretion and measurements of musculoskeletal change. Dr. Smith directed the SMS-II biostereometric effort for Technology Incorporated and performed the documentation of candidates for the Life Sciences Archives for use in future body measurements by the use of biostereometric techniques. He has been associated with the Biostereometrics Program since Apollo 16.

A CARDIOVASCULAR SPACELAB AND

BED REST STUDY

A Cardiovascular Spacelab/Bed Rest Study

Abstract

The purpose of this study is to document the cardiovascular changes which occur during spaceflight and bed rest, and to determine if bed rest is a realistic model for studying weightlessness. The experiment will be conducted in two phases: a ground phase and spaceflight phase. Each phase will consist of 3 parts, a 14 day amubatory control period, a 10 $\pm$ 2 day spaceflight or bed rest period, and a 14 day post experimental recovery period. A strict metabolic diet will be consumed by the subjects throughout the experiment. Information concerning the biochemical events commencing immediately after the start of bed rest or spaceflight will be obtained by collecting urine and blood samples. Total body water, plasma volume, extracellular fluid volume and red cell mass will be measured during the ambulatory control periods. Cardiovascular measurements will be made throughout the experiment. Changes resulting from fluid volume redistribution and muscle atrophy will be monitored using biostereometric analysis. By using the same crewmember, for both the bed rest and spaceflight portions of this experiment it will be possible to minimize individual variation as an interacting parameter in this study.

Applicable Life Science Speciality: Cardiovascular

A Cardiovascular Spacelab and
Bed Rest Study

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1.0 OBJECTIVES

1.1 Hypothesis

There is unequivocal evidence today that hypogravic stresses such as space flight, bed rest, and water immersion result in significant fluid redistribution within the body. The removal or minimization of the hydrostatic pressure in the blood column coupled with the normal tissue elastic forces and muscle tone of the lower body, results in shifts of blood and tissue fluid from the lower body to the intrathoracic circulation, with a consequent increase in central blood pressures and stimulation, of cardiopulmonary vasculature stretch receptors. This leads to a complex neuro-humoral response and rapid secondary changes in the cardiovascular and renal systems. The short term response is nearly opposite to the effects observed when subjects change position from supine to upright: a) sympathetic tone is reduced leading to peripheral vasodilation, b) increased venous return leads to enhanced cardiac output, c) secretions of renin, angiotensin, aldosterone and ADH are reduced, thus promoting vasodilation and elimination of water and salt, d) renal blood flow is increased as is urinary excretion of fluids and electrolytes, e) capillary pressures rise filtering fluid into the interstitial regions of the upper body, and f) drinking may be reduced due to a depressed thirst drive.

There is a reduction in plasma volume which serves to partially correct the pressure disturbance and leads to plasma concentration of red cells

and plasma colloids. At the end of the period of adaptation, the legs may have lost more than a liter of fluid. Other than the decreased leg volume, symptoms of head fullness and reduced drinking, none of these effects have actually been recorded during the early phases of space flight. Some of these changes have been observed in ground-based hypogravic stress studies and are expected in the current study. It is anticipated that the imposition of a -4° head-down tilt will more faithfully elicit the full spectrum of changes observed in prior space flight and anticipated in the Space Shuttle Program.

1.2 Background

Results of biomedical investigations performed during space flight indicate that exposure to weightlessness induces several metabolic and hormonal changes. These changes have been studied extensively, especially during the Skylab missions where an increase in the excretion of sodium and potassium together with loss of body fluid was observed. Plasma renin activity was also increased along with urinary excretion of aldosterone and other steroids (1,2).

In addition to the metabolic and hormonal changes, exposure to weightlessness also produces acute and possibly long term hemodynamic alterations. Astronauts have reported a feeling of head fullness and inflight photographs have documented the occurrence of puffiness of the face, distension of neck veins and other signs of fluid congestion in the head (3). In addition to these changes during the flight it has long been recognized

that decreased orthostatic tolerance develops postflight (4,5,6) and represents one of the dangers of flight. The cause-effect relationships between the metabolic and cardiovascular changes is unclear because the first inflight biochemical determinations were performed on the third or fourth inflight day after most of the initial alterations already had occurred.

Prolonged bed rest has been used by several investigators as a model of the weightless state (7). Changes in body position from vertical to horizontal minimizes the hydrostatic component of the blood pressure by reducing the height of the hydrostatic column to approximately one-seventh of its value in the erect position. A negative tilt, during which the head is lower than the rest of the body, has been used to simulate the effect of weightlessness on the cardiovascular system. A larger orthostatic hypotension developes in subjects exposed to a prolonged head-down position and it has been concluded that this position more accurately simulates weightlessness than the horizontal position (6).

Successful development of countermeasures to be used in long term space flight and reliable evaluation of their efficacy is primarily dependent on the selection of an adequate simulation method.

1.3 Relevance of Expected Results

This study will provide systematic documentation of the cardiovascular changes which occur during spaceflight and bed rest and will determine if bed rest is a realistic model for weightlessness. This information will be valuable when designing future experiments and in understanding the physiological changes which occur during spaceflight.

2.0 GENERAL APPROACH

The primary objective of this study is to determine the cardiovascular effects of bed rest and spaceflight and to determine if bed rest is a realistic model for weightlessness. By using the same crewmembers for both portions of the experiment it will be possible to eliminate individual variations as an interacting parameter in the study.

2.1 Experimental Design and Approach

This experiment will be conducted in two phases: a ground phase and a spaceflight phase, each phase consisting of three parts. The ground phase will consist of a 14-day ambulatory control period, a 10 $\pm$ 2 day bed rest period, and a 14-day recovery period. The flight phase will consist of a 14-day preflight ambulatory control period, a 10 $\pm$ 2 day spaceflight, and a 14-day postflight recovery period. The length of the bed rest study will be matched to the designated length of the space shuttle flight. During the bed rest treatment phase, the subjects will be placed in a 4° head-down tilt.

Strict adherence to the study protocol and metabolic diet will be required. Measurements of fluid intake and output will be performed each day. The subjects will also be weighed daily after a urine closeout at 7 a.m. $\pm$ 30 min.

During the ambulatory bed rest and flight control periods the subjects will be outpatients at the USPHS Hospital. They will adhere to their controlled diet and submit to all required physiological and biochemical test procedures.

The subjects will be hospitalized during the bed rest phase. They will not be allowed to use pillows or lift their heads, but will be permitted to turn on their sides or lie in the prone position. All eating and excretory functions will be performed while in the supine position. All subjects will feed themselves three time each day. During meals, subjects will be allowed to raise their heads on one elbow, but shall not exceed 30 cm. in height.

Restrictions

In order to obtain meaningful data from the study, the following restrictions will be placed on the subjects.

1. Water may be ingested ad libidum, but intake will be measured. Therefore, deionized water will be provided in measured quantities and intake will be restricted to only these supplies. Water from other sources may be used for brushing the teeth, but shall not be swallowed.

2. Subjects will be strictly limited to the prescribed diet. All supplied food must be consumed and spills should be reported promptly for replacement. Foods not consumed will be returned to the metabolic kitchen.

3. Subjects shall report all suspected illness events which occur during the study.

4. During the ambulatory phases of the experiment, subjects may not spend more than 1 hour in bed between 8 a.m. and 8 p.m.

5. During ambulatory phases, subject may engage in physical activity, but not at such a level as would produce pronounced sweating. Further, subject shall not remain in direct hot sun or in any environment which would produce high sweating levels.

2.2 Procedures

2.2.1 Subjects and Facilities

Ten mission specialist will be selected to participate in this study. A determination of lean body mass by estimating the natural abundance of ^{40}K and hydrostatic weighing will be performed prior to the study to determine the energy requirements of each subject.

All ground-based studies will be conducted in a temperature and humidity controlled metabolic ward at the USPHS Hospital in Nassau Bay or in the cardiovascular laboratories at the Johnson Space Center. While on the metabolic ward the subjects will be under constant observation by the nursing staff which is made up of specially trained nurses and paramedical personnel.

2.2.2 Nutritional Monitoring

Each day, subjects will be required to consume measured quantities of specific nutrients. Ground-based diets will consist of the same Space Shuttle foods which will be consumed inflight. The total energy content of this diet will be predicated upon an accurate estimate of each subject's lean body mass in accordance with published forumlae for energy utilization in weightlessness. Compliance with these nutrients requirements must be ascertained by analysis.

All nutrient analytical values will be ascertained either by reference to the information published by the manufacturer on the Nutrition Label and determined by the Food and Drug Administration to be in compliance with the Nutrition Labeling Regulations or will be obtained directly utilizing methods of the American Organization of Analytical Chemists (AOAC).

All foods will be derived from pre-analyzed lots. Menus will be constructed in such a way that each day each test subject will be provided with the recommended dietary allowance of each food and a constant calcium intake. If vitamin D is added to the food, or provided in the form of a supplement, it must be in the form of vitamin D_3. The intake of each food item must be recorded. If the food item is not consumed completely, the quantity of the residue must be estimated. With respect to the intent of this paragraph, "food" means anything taken into the mouth which contains any nutrient.

2.2.3 Urine Collection and Analysis

All urine voids will be collected individually throughout the entire study in order to preserve information about diurnal variations and the specific time course of biochemical events commencing immediately after the start of bed rest and spaceflight. Inflight sample volume will be measured, recorded, and a representative 5 ml. sample will be frozen for later analysis.

The inflight collection of the urine and fecal samples will be done by each subject using the Biowaste Monitoring System (BMS). The BMS contains the Urinary Monitoring System (UMS), and the Fecal Monitoring System (FMS). Both are currently under development. The BMS will collect and measure the mass of the urine or feces, remove air and particulate matter, and homogenize the urine or feces. Samples will then be collected, frozen, and stored. The measurement of the urine mass must be accurate to within 2%. Contamination of the collections must be limited to 5%.

The following laboratory analyses will be performed on these samples: volume, osmolality, specific gravity, calcium, inorganic phosphate, chloride, creatinine, sodium, magnesium, potassium, uric acid, anti-diuretic hormone, aldosterone, catecholamines, cortisol, and natriuretic activity.

2.2.4 Blood Collection and Analyses

Blood samples will be obtained by venipuncture from subjects who have been fasting for at least 8 hours and who have been supine for at least 30 minutes.

The inflight blood collection and sampling system (IBCS) will be similar to that previously utilized for spaceflight. The blood will be

collected by a payload specialist in a 25 ml tube. The blood will be separated into plasma and red blood cells by the Automatic Sample Processor and frozen for storage. Only the serum need be retained. Serum will be analyzed for: osmolality, sodium, cholesterol, triglycerides, magnesium, glucose, inorganic phosphate, potassium, chloride, calcium, uric acid, creatinine, creatinine phosphokinase, lactic dehydrogenase, ACTH, cortisol, angiotensin I, aldosterone, catecholamines, and total serum proteins.

Routine hematological and special hematological tests will be performed on all blood samples, including two 10 ml samples which will be collected on the fifth day of bed rest and two days after recovery. Routine hematologic tests will include: hemoglobin, hematocrit, white cell differential, white cell count, erythrocyte indices, and protein electrophoresis, including lipoprotein fractions.

Special hemotological tests will include: erythropoietin assay, 2.3-Diphosphoglycerate, p_{50} (50% oxygen saturation of hemoglobin), and reticulocyte age classification.

2.2.5 Body Fluid Compartment Analyses

Simultaneous measurements will be made of plasma volume, red cell mass, extracellular fluid volume, and total body water. These measurements will be performed on pre-flight and pre-bed rest days -14 and -7, immediately post bed rest, and postflight and on days +7 and +13.

Doses containing 2.0 μCi of ^{25}I human serum albumin, 25 μCi of ^{51}Cr labeled red cells, 25 μCi of sodium sulfate, 25 μCi of ^{3}H water, will be used for these studies. The ^{3}H is given orally and specific urine samples are assayed for the concentration of the radionuclide. All the other labeled compounds are injected intravenously and radioactivity is assayed.

2.2.6 Cardiovascular Measurements

An orthostatic stand test will be administered weekly during the pre-flight and pre-bed rest control period and during the recovery phases. The stand test will include measurements of heart rate, blood pressure, limb blood flow, leg volume, systolic time intervals, and VCG.

The measurement of the response to the anti-orthostatic stress includes heart rate derived from one component of the Frank System of vectocardiography. Systolic and diastolic blood pressures will be obtained from a blood-pressure measuring system that automatically cycles every 30 seconds during the stand test.

The blood-pressure-measurement system consists of an arm cuff with enclosed microphone, a pressurizing system, and associated electronics. Gating circuitry, triggered by signals from the VCG system, allows sound to be perceived only during an appropriate interval following each QRS complex. Filtering, amplication, and decision logic circuitry, based on an analysis of systolic and diastolic Korotkoff frequency spectra and

amplitude, identify systolic and diastolic sounds when certain ratio criteria are met and display them digitally. The systolic- and diastolic- design logic is designed to compare closely to the auscultatory method of blood-pressure determination. The programming circuitry is set to provide cuff inflation to 160 mm Hg and systolic and diastolic values every 30 seconds.

Blood flow is measured once a minute using an arm occlusive cuff to occlude venous return from the forearm. During the first 5 to 10 seconds of an occlusion cycle the expansion of the forearm is directly proportional to blood flow into that 1-inch segment of the forearm under the capacitance plethysmograph. Occlusion of the forearm is obtained by placing a standard arm blood-pressure cuff proximal to the elbow and inflating the cuff to a pressure of 50 mm Hg for twenty seconds. With a cuff controller, inflation is accomplished in less than 1.5 seconds. thus providing very rapid stoppage of venous return and an accurate measure of arterial inflow until back pressure slows the inflow. Programming of the cuff controller provides cyclically twenty seconds of venous occlusion followed by 40 seconds of unimpeded arm circulation.

Initial calibration of both arm and leg plethysmographs is obtained using the band on a series of calibration cyclinders of known size. Comparison of the capacitance plethysmograph with mercury stain-gauge plethysmograph has established a good verification of accuracy, reliability, and reproducibility. The leg measurements will be conducted with subjects supine and upright.

The VCG system utilizes the Frank lead placement of electrodes, with the exception that the right-leg ground and left-leg electrodes are placed over the right- and left-sacral regions, respectively. The heart rate is obtained by integration of time every five beats and displaying the rate in beats per minute on the VCG Digital Display. The VCG signal is digitized at 320 samples per second per channel and transmitted by pulse-code modulation telemetry. Thus rate can be obtained later either from the reconstructed VCG or the heart-rate signal sampled at a frequency of 1.-5 sps.

In addition to the cardiovascular measurements made during the stand test, heart rate, electrocardiographic activity and blood pressure will be monitored twice daily during space flight and bed rest. Limb blood flow will also be measured on selected days using the methods decribed above.

Other measurements of cardiovascular effects will be assessed by maximal treadmill exercise stress tests following each orthostatic stand test.

A continuous ECG/VCG will be employed with heart rate determined at 15 second intervals. Blood pressure as described above will be measured every 60 seconds during the test.

Heart volume changes will be accessed by comparing timed roentgenographic chest films from pre-bed rest and pre- spaceflight to immediately post bed rest and spaceflight.

Daily Measurements Schedule

AMBULATORY CONTROL

	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
HEMODYNAMIC MEASUREMENTS (BP, ECG, HR, BF)	o							o						o
BIOSTEROMETRIC ANALYSIS OF FORM														o
HEART VOLUME (X-RAY)														o
CARDIOVASCULAR RESPONSE TO STANDING AND EXERCISE*	o							o						o
URINE COLLECTION & BODY WEIGHT	o	o	o	o	o	o	o	o	o	o	o	o	o	o
BODY COMPARTMENT VOLUMES**	o							o						
BLOOD SAMPLE COLLECTION+	o							o						o
SAMPLE VOLUME(ml)	50							50						25

BED REST OR SPACE FLIGHT

	1	2	3	4	5	6	7	8	9	10
HEMODYNAMIC MEASUREMENTS (BP, ECG, HR, BF)	o	o	o	o	o	o	o	o	o	o
BIOSTEROMETRIC ANALYSIS OF FORM										
HEART VOLUME (X-RAY)										
CARDIOVASCULAR RESPONSE TO STANDING AND EXERCISE*										
URINE COLLECTION & BODY WEIGHT	o	o	o	o	o	o	o	o	o	o
BODY COMPARTMENT VOLUMES**										
BLOOD SAMPLE COLLECTION+	o	o	o		o		o		o	
SAMPLE VOLUME(ml)	25	50	25		25		25		25	

AMBULATORY RECOVERY

	R0	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13
HEMODYNAMIC MEASUREMENTS (BP, ECG, HR, BF)	o	o	o					o						o
BIOSTEROMETRIC ANALYSIS OF FORM	o													
HEART VOLUME (X-RAY)	o													
CARDIOVASCULAR RESPONSE TO STANDING AND EXERCISE*	o	o	o					o						o
URINE COLLECTION & BODY WEIGHT	o	o	o	o	o	o	o	o	o	o	o	o	o	o
BODY COMPARTMENT VOLUMES**	o							o						o
BLOOD SAMPLE COLLECTION+	o							o						o
SAMPLE VOLUME(ml)	50							50						50

*Cardiovascular Response to Standing Includes Measurements of Heart Rate, Blood Pressure, Forearm Blood Flow, Leg Volume, Systolic Time Intervals, and VCG.

**Body Compartment Volumes Includes Measurements of Total Body Water, Plasma Volume, Extracellular Volume, and Red Cell Mass

2.2.7 Biostereometric Analysis

A biostereophotogrammetric procedure will be used to derive the Cartesian coordinates of numerous points on the body surface. From these the surface area and volume of the body will be computed as well as the volume of body segments and the area and shape of cross sections. Changes resulting from fluid volume redistribution and muscle atrophy can be monitored by these means. Each subject will be studied at approximately the same time of day, after breakfast, but before any strenuous physical exercise. Measurements will be made immediately before and after bed rest.

Two sets of stereometric cameras are used to photograph the front and back of the subject simultaneously. A strobe projector, mounted midway between the cameras of each stereopair, illuminates the subject with a random pattern of lines, enhancing the plottability of the skin surface. Two calibration units are used to determine the scale factors in the 3 orthogonal axes. Each subject wearing an elastic skull cap and an abbreviated athletic supporter, stands in a similar pose so that differences due to changes in posture are minimized. He places his feet on "foot print" patterns to achieve standard leg separation, and holds his arms straight, with flattened palms toward the rear approximately 10 cm from the thighs. The exposures taken on metallographic glass plates are made at the moment the subject is judged to have fully exhaled.

The glass plates are enlarged to 10 x 10 in and placed in a Kern PG-2 stereoplotter which, through a metrigraphic terminal, punches the

coordinates on IBM computer cards. The scales in the three orthogonal planes are derived from steel tapes and rods of known length attached to the calibration units. The front and back stereopairs are scaled independently. Plotting of the subject begins with the highest point of the head for the front stereopair and moves from side to side working downwards. Successive plotting levels are determined from the markings on the steel tape. The levels are separated by 4 cm over most of the body and by 2 cm in areas where the cross-sectional area is changing rapidly. The same tape is used to fix plotting levels for the back stereopair, thereby assuring a match between the levels for the front and back of the body.

The card deck is processed by a computer program which calculates the scale factors, shifts front and back coordinates to a common coordinate system, converts the raw coordinates into centimeters, matches the fronts and backs, and outputs to magnetic storage a level-by-level coordinate description. Cross-sections of each level are plotted on microfilm and examined. Any stereoplotting errors which may be found are corrected, and frontal and profile views are then plotted on graph paper by a program using the processed level-by-level data.

With a computer program, the cross-sectional area of the body at each plotted level is calculated. Areas invisible to the cameras are interpolated. Curve-fitting techniques are used to derive the cross-sectional area at 1 mm intervals over the head and trunk, and both arms and legs.

The volume of a body segment under examination is calculated by integrating the cross-sectional areas between the previously determined landmarks. Volume comparisons shown as percent change will be made between the pre-bed rest value and each of the post bed rest values for the arms, chest, abdomen, buttocks, thighs, and calves for all 10 subjects.

2.2.8 Data Analysis System

An automated integrated data base, analysis and simulation system simular to that used for Skylab analysis will be employed in this study. The system consists of mass storage elements for experimental data, statistical software for routine and non-routine data analysis, special purpose data processing programs, several previously validated simulation models and the terminals and graphic display units for accessing these elements. This system will provide investigators with a means of rapidly scanning data, transforming, combining and editing data for analysis, and performing regressions, correlations, and other statistical tests. In addition, the system provides needed clinical and environmental parameters on any test day and the capability to retrieve, analyze, and display simulation model output simultaneously with the data.

The analysis system for this study will include:

a. Mass storage for all experimental data.
b. Interface with graphic display remote terminals for interactive use.
c. Interface with descriptive statistics package (means and variance) for pooled data.

d. Interface with advanced statistical package (analysis of variance, trend analysis, time-series analysis, curve fitting procedures).

e. Interface with model output to provide graphic display of results in comparison with simulation results.

f. Interface with other ground-based data bases.

2.2.9 Statistical Analysis Approach

Prior to conducting this study, statistical models will be established and the objectives of the experiment will be formulated in terms of these models. This pre-study analysis will also assist the investigators in establishing controls, number of samples required from each subject, number of replicate analysis, establish desired accuracy of instrumentation in accord with expected results, and define the preferred methods of statistical analysis.

It is anticipated that subsequent to the bed rest study, the following analyses will be performed:

a. Analysis of variance between pre-study, supine or space flight, and post-study phases for all data.

b. Trend analysis and time-series analysis for all appropriate data to search for significant trends regarding magnitude and frequency of response.

c. Multiple regression analysis to search for significant correlations between logical groups of variables. For example, hormonal responses may be correlated with electrolyte and fluid volume changes.

2.2.10 Data Reporting

The following requirements for information gathering and reporting have been identified.

1. Formatted data sheets will be used to report all common data.
2. All transmitted data will be typed and verified.
3. The following information will accompany each measurement value:
   a. Subject identification
   b. Time of day of measurement
   c. Treatment phase (i.e., control, bed rest, spaceflight, post-bed rest, post-flight, experimental maneuver)
   d. Sequence number of measurement if part of serial measurements performed on any signal day.
4. Individual measurement values for each subject will be reported. If samples are analyzed in duplicate or triplicate, the mean and variance for that measurement will be reported.
5. A patient biomedical history will be provided for each subject including history of smoking, drugs, disease, physical activity, psychological behavior, recent weight changes or lifestyle changes.
6. A patient monitoring record will be kept for each subject reporting any events or activities deviant from standard protocol; sleep-wake record, activity record, etc.
7. An environmental parameter record will be kept, reporting dry bulb temperature, humidity, lighting level, and atmospheric pressure, for each day.

8. Diet for each 24-hour period will be reported in term of nutrient intake. *Ad libitum* water intake will be monitored and reported as 24-hour pooled volumes.

2.2.11 Model Simulation Analysis

Mathematical model simulation has proven to be a unique technique in the interpretation of space flight data. A group of these models of the thermoregulatory, cardiovascular, respiratory, fluid-electrolyte and erythropoiesis systems have been utilized to identify and evaluate hypotheses, predict dynamic responses not amenable to measurement, integrate data from various investigative areas and define data analysis requirements. These models have been used both separately and in combination with each other; in the latter case, the whole-body algorithm is capable of simulating prolonged space flight including the periodic metabolic and cardiovascular stress tests. The simulation models can be considered a collection of integrated theories and empirical relationships against which a large protion of experimental data can be compared, evaluated and tested for consistencies or discrepancies. This is an interative process cycling between experimentation and simulation. As a crucial element, the experimenter or analyst can thereby develop, modify and refine the hypotheses of which the model is composed as well as visualize the dynamic physiological changes in the responses of the total system due to the hypotheses. This approach should be regarded as complementary to the traditional statistical method of processing experimental data.

The simulations planned to support this study include the following:

1. Simulation of Circulatory, Fluid, Electrolyte Response

   Model: Guyton's model of fluid-electrolyte control

   Purpose: Given water and electrolyte intake and leg volume changes, model can predict changes in fluid compartments, electrolytes, plasma levels of hormones, renal function, circulatory indices.

   Input Data Required:

   a. Leg fluid volume changes
   b. Plasma protein
   c. Hematocrit
   d. Urine volume
   e. Urine Na^+ and K^+
   f. Urine ADH, aldosterone, angiotensin
   g. Plasma aldosterone and angiotensin
   h. Plasma Na^+ and K^+
   i. Circulatory Parameters
   j. Body compartment volumes

      Plasma Volume

      Extracellular Volume

      Total body water

2. Simulation of Exercise

   Model: Pulsatile Cardiovascular Model

   Purpose: To investigate the mechanisms producing orthostatic intolerance

TABLE 1

PHYSIOLOGICAL QUANTITIES DERIVED FROM COMPUTER MODELS

I. METABOLIC BALANCE MODELS CORRECTED BY TOTAL BODY MEASUREMENTS

- DAILY EVAPORATIVE WATER LOSS
- DAILY TOTAL BODY WATER
- DAILY TOTAL BODY SODIUM
- DAILY TOTAL BODY POTASSIUM
- DAILY TOTAL BODY NITROGEN
- DAILY PROTEIN AND FAT CHANGES
- MEAN ELECTROLYTE SWEAT LOSSES

II. ERYTHROPOIESIS CONTROL SYSTEM MODEL

- DAILY PLASMA VOLUME
- DAILY RED CELL MASS
- DAILY BLOOD VOLUME

III. LONG TERM CIRCULATORY, FLUID, ELECTROLYTE SUBSYSTEM OF WHOLE-BODY ALGORITHM

- DAILY INTRACELLULAR/EXTRACELLULAR FLUID VOLUMES
- DAILY INTRACELLULAR/EXTRACELLULAR ELECTROLYTE CONCENTRATIONS
- DAILY PLASMA LEVELS OF ALDOSTERONE, RENIN, ANGIOTENSIN, ADH
- DAILY RENAL EXCRETION OF FLUIDS/ELECTROLYTES
- DAILY CIRCULATORY INDICES: FLOWS, PRESSURES, RESISTANCES

IV. SHORT TERM SUBSYSTEM OF WHOLE-BODY ALGORITHM

- LBNP AND EXERCISE RESPONSE (PRESSURES, FLOWS, HEART RATE, LEG VOLUMES) AS A FUNCTION OF MISSION TIME
- EFFECTS OF TRAINING ON EXERCISE PERFORMANCE

Data Required:

Measure HR, systolic, diastolic pressure and leg volume

Cardiac Output

2.3 IMPLEMENTATION REQUIREMENTS

2.3.1 Facilities

Ground-based studies will be conducted at the USPHS Hospital in Nassau Bay, and at the NASA/JSC cardiovascular laboratory. The use of space and x-ray facilities at NASA/KSC will be required for the immediate preflight and postflight measurements.

2.3.2 Equipment

The following items of equipment will be required for the ground-based studies:

a. Climate Controled Metabolic Ward

b. Normal Clinical and Laboratory Equipment

c. Biosteriometric Equipment

d. Real time computer data analysis

e. ^{125}I, ^{51}Cr, Sodium Sulfate, ^{3}H

f. Treadmill ergometer and associated equipment

g. Inflight Blood Collection Equipment

h. Biowaste Monitoring System (BMS)

i. Skylab type Experimental Support System for Cardiovascular Measurements

j. Venous occlusion forearm blood flow equipment

k. Radiographic equipment

Inflight equipment requirements are all part of Life Sciences Laboratory Equipment. They will consist of the BMS for urinary samples, and the inflight blood collection and sampling system and centrifuge for plasma samples. A skylab type experimental support system for cardiovascular measurements, and venous occlusion forearm blood flow equipment.

2.4 Operational Requirements

The performance of this experiment inposes no constraints on the orbital flight.

2.5 Payload Specialist Requirements

A payload Specialist will be required who is trained in obtaining blood samples and cardiovascular testing. All other inflight procedures will be accomplished by the individual flight crewmember. Crewmembers participating in this study will not take part in any scheduled exercise routine.

2.6 Critical Constraints

none

2.7 Problem Areas

none